The Archives of Internal Medicine

Vol. XVIII SEPTEMBER, 1916. No. 3

DISSOCIATED JAUNDICE *

C. F. HOOVER, M.D., AND M. A. BLANKENHORN, M.D.
CLEVELAND, OHIO

The subject of dissociated jaundice has been discussed by a number of French physicians during the past five years. There have been in all about thirty articles on the subject published in French medical journals. A fairly complete bibliographic reference will be found in an article by Lemièrre, Brulé and Garban.[1]

In all the published articles there are several weak points for criticism. There was not sufficient correlative control of biliary elements in the plasma and urine. The adsorptive property of plasma for bile salts as well as bile pigment was not clearly perceived. As will be seen from our observations, the plasma may under some conditions, not yet clearly understood, retain a large amount of bile pigment and yield none of it to the kidney, although the kidney function may be perfectly normal. This adsorptive property of the plasma may hold bile pigment so firmly in its grasp that no pigment will be yielded to the tissues, so the disparity between icterus of the plasma and icterus of the skin may in some few instances be as striking as the disparity between cholemia and choluria. Adsorption of bile salts is not nearly so marked as adsorption of bile pigment, but in primary anemia, particularly, the presence of bile salts in the plasma without the presence of bile salts in the urine has been abundantly confirmed in our experience.

And, finally, without some improvement over the old method of separating bile salts from the plasma, it is impossible to make any progress in the clinical studies of jaundice. The older methods of separation were too time consuming, too uncertain, and required too much plasma for routine clinical work. The use of the collodion sack as a dialyzer affords a very simple, and we believe the most delicate, method thus far proposed for the purpose.

The term "dissociated jaundice" carries with it the inference that either the pigment or the salts of bile formed within the liver are separately shunted from the biliary path into the lymph or blood ves-

* Submitted for publication June 5, 1916.

1. Lemiérre, Brulé and Garban: Les retentions biliaires par lesion de la cellule hèpatique, Semaine méd., 1914, xxxiv, 301.

sels of the liver. We have succeeded thus far in showing that bile salts may be shunted in this manner, but we are not yet certain that bile pigment formed in the liver is separately shunted into the blood stream. This is what we should a priori expect when we consider the comparative facility with which the salts will pass through a dialyzing membrane, as shown by the concentrations of bile required to yield pigment and bile salts, respectively, to the dialysate when collodion sacks are employed for dialysis, and also when we consider the fact that the renal filter will yield bile salts to the urine from a lower grade of cholemia than is required for bile pigment to appear in the urine.

There have been several causes which have delayed the analysis of this very common problem in clinical pathology. Medical men generally have been for many years misled by the erroneous interpretations of jaundice made by Stadleman and Naunyn and Minkowski, who arrived at the very definite conclusion that there can be no jaundice without the agency of the liver. According to these observers, all jaundice is hepatogenic, and hematogenic jaundice does not exist. Although many clinicians have been skeptical toward the teaching that all icterus is hepatogenous, the first satisfactory experimental evidence of the truth of hemolytic icterus I have found is that of Lyon-Caen,[2] 1910, and the final absolute proof of extra hepatic jaundice was given by Whipple in 1916.

Briefly stated, the following problems are to be solved in the clinical study of icterus. If pigmental cholemia is present without bile salts, the pigment may originate from the formation of bilirubin from hemoglobin within the blood vessels, as occurs in hemoglobinemia from any cause; or after complete cholemia of hepatic origin the bile salts have been yielded to the kidney and the adsorbed bilirubin remains fixed to the plasma. The latter instance is not dissociate jaundice of hepatic origin, but is merely separation of the two biliary elements by renal elimination of the bile salts. When bile salts without bile pigment are found in the plasma, we are bound by our present knowledge to assume there exists a genuine dissociate jaundice of hepatic origin. For thus far there are no clinical or experimental evidences to show there can be an extra hepatic origin of bile salts, and in all our experimental and clinical studies we find no evidence that bile pigment can be eliminated through the kidney and bile salts retained in the plasma. If the two biliary elements are separated by renal elimination, it will always be bile pigment which will be retained in the plasma and not bile salts. To avoid confusion in using the term "dissociation icterus" it will be advisable to employ a terminology which will indicate the source of the dissociation of biliary elements in the plasma. "Complete icterus" will mean the presence of bile pigment and bile salts in the

2. Lyon-Caen: Jour. de physiol. at de pathol. gén., 1910, xii, 526, 758.

blood. "Hemolytic icterus" implies the presence of bilirubin in the blood without bile salts, when bilirubin is formed extra hepatically. "Hepatic dissociation icterus" implies the presence of bilirubin or bile salts separately in the plasma, due to one or the other of the bile elements being separately shunted into the blood stream. By "renal dissociation icterus" we mean the presence of bile pigment in the plasma due to separation of the biliary elements through renal filtration of the bile salts.

METHODS OF STUDY

The simplest and best method of detecting bilirubin in blood plasma is Gmelin's test. Between the white coagulum and the underlying nitric acid there is a yellow granular zone. Within the white coagulum there will be seen a line more or less broad, varying with the concentration of bile in the plasma, which has a distinct blue-green color. This blue-green line will appear immediately in high concentrations of bile, but in the very low concentrations of bile in the plasma the blue green line will not appear until after a lapse of half an hour. After the test has stood for a longer time, the white coagulum will ascend in the zone of plasma, but will always preserve the same thickness. The blue-green line holds its relative position in the white coagulum as this ascends, and the lower yellow zone increases in depth as the coagulum ascends.

The best method of detecting bile salts in the plasma we have found in the use of collodion sacks. A mixture of equal parts of alcohol and water is the best medium with which to surround the collodion sack containing the plasma.

In testing for bile salts we use two or three dialyzers, each containing about 5 c.c. of plasma. After the dialyzers have stood for twelve hours, the several dialysates are concentrated, and then the concentrated dialysate is tested with Pettenkofer's method. Simply the color test and spectroscopic absorption band in the purple can not be accepted as proof of the presence of bile salts. If no further criticism is employed, there is great danger of accepting a test as positive which is really spurious. We have adopted the plan of accepting as positive only those tests which give the characteristic color reaction to furfurol and sulphuric acid; then the spectroscopic examination of the reaction will give an absorption band in the purple. After the reaction stands for twelve hours or more a darker purple color supersedes the original pink reaction, and then spectroscopic examination will reveal a disappearance or diminution of the original absorption band in the purple and the appearance of a new, sharply defined band in the orange. The alteration in color on standing and the movement of the absorption band into the orange are essential to prove the correctness of a Pettenkofer test. The dialysate from many serums will give the original pink color

and purple absorption band, but when the reaction is allowed to stand, it will not change to the pink-purple color; neither will the absorption band move over to the orange. This further observation in the Pettenkofer test has saved us from making many errors in detecting bile salts in the plasma. Without this control we would have pronounced many tests as positive which were really spurious.

We find the collodion dialyzer to be a great aid in detecting bile salts. It is a very simple method and is much preferable to the old method of separating the bile salts from the protein by repeated precipitations and filtering and washing, which is practiced in the Hoppe-Seyler method. Much less serum is required for the process, and in the Hoppe-Seyler method the Pettenkofer reaction is the final test, just as we employ it with the dialysate from the plasma. The delayed spectroscopic control is applicable to the Hoppe-Seyler method of separation of the bile salts as well as in our method of separation by means of the collodion dialyzer.

We tried electrolytic dissociation to detect bile salts in plasma, but met with no success. The dialyzer is much simpler and much more delicate. To procure bile salts from a solution by electrolysis requires a much higher concentration of bile salts than we find in the plasma of jaundiced patients.

We have found the collodion dialyzer and the spectroscopic control of the Pettenkofer test equally important. Both these measures have been essential to our clinical analyses of jaundice. Without a satisfactory method of detecting bile salts in plasma no progress can be made toward a study of dissociated icterus.

A review of the literature on dissociated icterus will show how the want of a satisfactory method for isolating bile salts from the plasma has hindered the progress of clinical studies of jaundice.

BILE SALTS AND PIGMENT IN THE URINE

Hammersten's method is the most satisfactory means of detecting bile pigment in the urine. This is the method we always employ when any case is reported as a positive test for bile pigmentation in the urine. Bile salts in the urine have given us more trouble than in the plasma. Pettenkofer's test is not so satisfactory as Hay's sulphur test, which can be inspected most satisfactorily when viewed from underneath the surface of the urine by aid of an electric lamp held between the observer's eye and the specimen which is being examined. The sulphur test is very delicate and simple and gives unequivocal results. We did not go far in studies of cholemia and choluria before we were impressed with the striking inconsistencies between these two conditions. For instance, in primary anemia we have studied fourteen cases and we failed to find bile pigment or bile salts in the urine in a single instance,

although all the patients examined had bile salts or bile pigment or both in the plasma. It is surprising to see how high a concentration of bile pigment will occur in the plasma of primary anemia without choluria.

In hemolytic jaundice with infection and without infection it is also surprising to see how deeply jaundiced the plasma will become without bile pigment appearing in the urine. This is the one point which serves to distinguish obstructive jaundice from other sources of jaundice. In obstructive jaundice the bile pigment appears in the urine much more promptly and with much lower concentrations of bilirubin in the plasma than must occur in hemolytic jaundice before the urine becomes bile stained. We find an unvarying consistency in the behavior of bilirubin toward the collodion dialyzer (with rather thick wall) and toward the renal filter.

If a patient has bilirubin in his blood and none in his urine, the dialysate from his plasma will contain no bilirubin. If bilirubin occurs in both plasma and urine, the dialysate will contain bilirubin. We have had only one experience which was apparently an exception to this rule. The patient had severe hemolytic dissociated icterus caused by streptococcus infection. The plasma was deeply stained with bilirubin, but no bilirubin could be found in the urine. The plasma dialyzed bilirubin in large amounts. The disparity in this instance was traceable to a severe disease of the renal filter, as shown both clinically and at necropsy. During life the alveolar air had a carbon dioxid partial pressure of 26.7 mm. of mercury. The nonprotein nitrogen of the blood was 0.076 gm. per 100 c.c. of blood. The carbonates of the blood by Van Slyke's method were 37.9 c.c. per 100 c.c. of blood. It seems very reasonable in this case to ascribe the apparent exception to the rule to the impermeability of the renal filter.

When bilirubin from the plasma passes neither the renal filter nor the collodion sack, the phenomenon is due to adsorption of pigment by the plasma. We showed in one of our first clinical studies of a case of dissociated hemolytic jaundice due to secondary syphilis that the renal filter was unimpaired; not only was there a want of all evidence of impaired renal function on the part of the urine and blood, but at the same time the plasma was so deeply jaundiced as to give a very strong Gmelin's test and no bilirubin occurred in the urine, while the phenolsulphonephthalein test for renal function was perfectly normal. Unfortunately the phenolsulphonephthalein test was neglected in the streptococcus case, which gave us the single exception to consistency of behavior toward bilirubin on the part of the renal filter and the collodion sack.

The importance of adsorption of bile pigment in blood plasma is very significant in another phase of jaundice. We find the plasma deeply stained with bilirubin in some cases of primary anemia when

there is not only no bilirubin in the urine, but no trace of jaundice to the skin or sclera. This has occurred in several cases of primary anemia with complete cholemia and also in hemolytic dissociated cholemia. In several of these cases the cholemia was of such intensity that a like degree due to obstructive jaundice would invariably cause choluria and jaundice. From the pronounced disparity between cholemia, choluria and jaundice of the skin and the varying disparity in different sources for jaundice, it seems very clear that the degree of fixation of bilirubin to the plasma depends on some chemical alteration in the protein or lipoids of the plasma.

Furthermore, we are impressed with the fact that a large amount of bile pigment and also bile salts may be in the plasma and entirely disappear from the plasma without either salts or pigment making their appearance in the urine. A priori, we should say in view of all these facts that the plasma has the first call on the biliary elements and holds them with considerable tenacity away from the renal filter and in some instances away from the tissues also. This adsorption of bile pigment by the plasma readily accounts for the disparity generally seen between the concentration of bilirubin in the serum of ascitic fluid and pleural fluid and the subarachnoid fluid, on the one hand, and the concentration of bile pigment in the blood plasma in cases of jaundice, and it also accounts for the fact that large amounts of bilirubin may be found in the serum of fluid contained in the pleural cavity in cases of hemothorax without bilirubin appearing in the plasma of the circulatory blood. In other words, whether the bilirubin is adsorbed primarily to plasma within or without the blood vessels the plasma does not yield the bilirubin to the vessel wall any more readily than it is yielded to the renal filter or to the collodion sack. However, if we have a normal plasma and a normal liver the bile pigment and bile salts are readily yielded to the liver, as is clearly shown by animal experiment. The Gmelin test for bilirubin in plasma is not sufficiently delicate to give the blue-green zone in the coagulum when bile is added to the plasma in sufficient amounts to give a visible yellow stain to the plasma. So the best method is to compare the plasma of an animal, before the injection of bile into the blood, with the plasma after the injection into the vein has been made.

The concentration of bile varies greatly. In order to give us some conception of the pigment concentration of a specimen of bile and also to give some comparative idea of the quantitative value of bilirubin concentration in plasma, we record what proportion of bile or cholemic plasma must be added to a column of water 1 cm. deep to give a visible yellow tinge to the water.

When we refer to a specimen of bile as having a concentration of 1 to 100 or 1 to 3,000 and a specimen of cholemic plasma as having a

value of 1 to 20 or 1 to 100, we mean that that proportion of bile or plasma respectively must be added to a 1 cm. column of water to give a visible color.

Experiment 1.—Into the brachial vein of a dog weighing 17,000 gm. 40 c.c. of human liver bile were injected. This bile had a color value of 1 to 1,000. Estimating the circulatory blood in the dog at 1,300 c.c., we get a proportion of 30 to 1,000 of bile to blood. Oxalate plasma, procured by tapping the dog's heart five minutes after the injection of bile, had exactly the same color as the oxalate plasma procured immediately before the injection of bile. The plasma gave a negative reaction to Gmelin's test. Hueppert's test for pigment and the dialysate gave a doubtful reaction to Pettenkofer's test for bile salts. Five minutes after the first injection of bile, 40 c.c. more of bile were injected into the vein, and in another five minutes a third specimen of oxalate plasma was procured by tapping the cava. This plasma had a slightly jaundiced hue and gave a positive reaction for bilirubin to Gmelin's and Hueppert's tests and the dialysate gave a slight reaction for bile salts to Pettenkofer's test. The urine procured from the dog's bladder contained no biliary elements.

From previous experiments we found that after intravenous injections of bile the dogs had diarrhea with intestinal hypercholia. This suggested that the reason why the dog's plasma was not stained with bile was because the liver had the first call on bile pigment from the plasma when the plasma and liver were both normal.

Experiment 2.—Under scopolamin and ether anesthesia the abdomen of a dog weighing 13,000 gm. was opened and the superior mesenteric artery and the trunk of the portal vein were clamped to throw the biliary function of the liver out of commission. When this had been done 20 c.c. of human liver bile with a color value of 1 to 1,000 were injected into the femoral vein immediately after a specimen of oxalate plasma had been taken and found to contain neither bile pigment nor bile salts. Two minutes after the 20 c.c. of bile were injected a second specimen of oxalate plasma was taken. This specimen had a slightly jaundiced color and gave a positive test to Gmelin's reaction. There were neither pigment nor bile salts in the dialysate from the plasma.

Seven minutes after the first injection of bile a second injection of 20 c.c. was made and two minutes thereafter a third specimen of plasma was procured, which showed a distinct increase in the yellow color and a much stronger Gmelin reaction than in the preceding specimen.

When the liver was eliminated from the circulation, the animal's plasma was stained with bile about as one would expect it to be stained were the same concentration of bile in plasma made in vitro.

Experiment 3.—We then undertook to eliminate the liver, inject bile into the veins and then release the clamps on the superior mesenteric artery and portal vein to see how promptly the bile would disappear from the blood. From a dog weighing 6,500 gm., under scopolamin and ether anesthesia, specimen 1 of plasma was procured. The abdomen was then opened and the superior mesenteric artery and the portal vein were clamped. Then 30 c.c. of human bile, 1 to 1,000, the same as in Experiments 1 and 2, were injected into the femoral vein. Five minutes after the injection of the bile, Specimen 2 of oxalate plasma was procured, and five minutes thereafter Specimen 3 was taken. Then the clamps on the superior mesenteric artery and portal veins were released and the mesenteric and portal flow of blood were reestablished. During the procedure the pulse volume changed very little, so there could have been little change in the minute volume of blood through the heart and the hepatic artery. Five minutes after Specimen 3 was procured, Specimen 4 was taken. In five minutes more Specimen 5, and in ten minutes Specimen 6, of the plasma was procured.

The results of examination of the plasma gave:

Specimen 1, clear and colorless.

Specimen 2, clear, distinctly yellow; Gmelin's test positive; dialysate with faint color and bile salts positive.

Specimen 3, clear, yellow; Gmelin's test positive; dialysate with faint color; bile salts positive. The clamps on the artery and the vein were released.

Specimen 4, clear, slightly yellow; Gmelin's test negative; dialysate had no color; bile salts positive.

Specimen 5, clear, less yellow than 4. Gmelin's test negative; dialysate had no color; bile salts negative.

Specimen 6, clear, very slight yellow; Gmelin's test negative; dialysate had no color; bile salts (?).

We then proposed to see what results a temporary obstruction of the common bile duct would give in a comparative study of the biliary elements in the plasma and in the urine. In six trials we succeeded in getting one successful experiment, in which the catgut ligature on the common duct was absorbed and the path of the common duct reestablished, as was shown at necropsy on the dog. The common duct of a dog was ligated with catgut and nine specimens of oxalate plasma were procured by heart puncture from ten to 192 hours after the ligation of the duct. Each specimen of plasma was dialyzed. Seven specimens of urine were procured from twenty to 100 hours after the duct was ligated. The concentration value of the bile pigment in the plasma was determined. The Pettenkofer test for bile salts was employed in the dialysate from the plasma. In the urine Hammersten's test was used for bile pigment and Hay's test was used for bile salts.

The results on the plasma and the urine are shown in Tables 1 and 2, respectively.

TABLE 1.—Effect on the Plasma of Ligation of Common Duct

Specimen	Time after Ligation of Common Duct, Hr.	Color	Gmelin Reaction	Concentration of Pigment	Dialysate	
					Pigment	Salts
1	10	None	0	0	0	0
2	28	Slight	+	1 to 50	0	+
3	48	More yellow	+	1 to 60	0	+
4	72	Increase	+	1 to 80	0	+
5	100	Less	∓	1 to 50	Lost	Lost
6	120	Less	0	0	0	?
7	144	Very faint	0	0	0	?
8	168	Fainter	0	0	0	+
9	192	Still perceptible	0	0	0	+

From these results it is seen that in temporary obstruction of the common duct, although there was a marked cholemia for both pigment and salts, there was no choluria for bile pigment at any time, although bile salts continued in the urine during the entire period of 100 hours after ligation. At the same time there was marked pigment cholemia without pigment choluria. The dialysate from the plasma contained no pigment at any time, but always contained bile salts, as did the urine.

TABLE 2.—Effect on the Urine of Ligation of Common Duct

Specimen	Time of Ligation, Hr.	Bile Pigment	Bile Salts
1	20	0	0
2	28	0	0
3	36	0	+
4	48	0	+
5	72	0	+
6	96	0	+
7	100	0	+

The dog had a slight icteric hue to the conjunctiva, but the icterus was not marked and would have borne a doubtful interpretation in consideration of the fact the urine contained no bile pigment. If only the scleral icterus and urine had been considered, the picture would have been that of a dissociate jaundice in which bile salts were dissociated from bile pigment. The examination of the plasma, however, showed the dissociation was purely a renal dissociation, and not a hepatic dissociation.

Obstructive jaundice in patients may be interpreted as cases of hepatic dissociation jaundice, if the urine and plasma should be examined during a period of remission.

One of our patients had gallstones with jaundice. The plasma showed an abundance of bilirubin, 1 to 100, and a positive Gmelin test. The urine also contained bile pigment, but there were no bile salts demonstrable in the plasma or in the urine. There was no reason for suspecting a hemolytic jaundice and there were no evidences for hepatitis. The urine at the time of the observation contained only 1 per cent. of the total nitrogen in the form of ammonia, and no urobilin.

The plasma and urine were examined after an acute obstruction had subsided, and on this occasion we found only the adsorbed bile pigment, which was only a survival of a complete jaundice from obstruction. Had the findings in the plasma and urine been considered apart from the clinical history and physical findings, we should have interpreted the case as one of hemolytic jaundice, but when the previous removal of gallstone and prompt recovery from jaundice and the want of any signs of hepatitis were considered, it was quite apparent we were dealing with a renal dissociation of bile salts from the bile pigment which survived in the plasma in a state of adsorption.

Another case of gallstone lodged at the junction of the cystic and common ducts gave similar findings at one examination. When first examined the patient was icteric. The urine contained bile pigment

and bile salts. The plasma was icteric, 1 to 100, and gave a positive Gmelin test. The aqueous dialysate contained both pigment and bile salts in abundance. Fifteen days later the urine contained neither bile salts nor bilirubin and the plasma had a concentration of bile pigment of 1 to 50 and gave a positive Gmelin reaction. The water and alcohol dialysate from the plasma contained bilirubin, but gave only a doubtful reaction for bile salts.

The patient made a prompt recovery after the gallstone was removed by operation. In this instance we again have the renal dissociation of salts from bile pigment in the blood. The bile pigment survived in the plasma after obstruction which originally produced complete jaundice. The following case was apparently an obstructive jaundice attending an acute gastroduodenal inflammation:

The patient was a vigorous young man 21 years old, who came under observation on the third day of his illness, which began with nausea, vomiting, anorexia and jaundice, with a normal temperature. On entering the hospital, the liver was not enlarged or tender. There was moderate jaundice and the stools were clay colored. The mercuric chlorid test to the stool gave only a very faint reaction after standing twelve hours. The intestinal hypocholia was very marked. The duodenal tube was passed into the doudenum and gave only very slight evidences of bile in the duodenum. Microscopically the duodenal content revealed many epithelial cells and an abundance of bacteria. The stomach secretion contained no free hydrochloric acid. The urine contained an abundance of bilirubin and bile salts, but no urobilin. The oxalate plasma was jaundiced with a color concentration of 1 to 100, and Gmelin's test was positive. The aqueous dialysate contained much bilirubin and an abundance of bile salts. Eight days later the jaundice was much diminished. The duodenal contents showed a marked increase in the amount of bile. The urine contained no bilirubin and no bile salts or urobilin. The oxalate plasma still showed the same concentration of bilirubin, 1 to 100. Gmelin's test was strongly positive.

On this occasion alcohol and water, equal parts, were used for the dialysate and the dialysate contained both pigment and bile salts. This was an apparent exception to the rule that bilirubin in the plasma behaved toward the collodion sack as toward the kidney. But as we learned later in our experience that comparisons between the permeability of the collodion sack and the renal filter should be made with water as a medium around the sack and not with alcohol and water, this can not be regarded as a fair exception to the rule, namely, that bilirubin in the plasma has the same threshold to renal filter and collodion sack.

Thus far we are justified in saying that in obstructive jaundice there may be cholemia without choluria and also there may be a renal dissociation jaundice of the plasma if the blood should be examined at a suitable time after the retention of bile (from the liver) has ceased

HEMOLYTIC JAUNDICE

The first patient with a clear hemolytic jaundice whom we studied was a woman who was profoundly anemic from a profuse hematemesis (ulcer). Transfusion was employed to combat the anemia. The husband acted as donor. Severe hemolysis followed the transfusion, as was shown by the chocolate colored urine, due to hemoglobin.

The following morning, twelve hours after the transfusion, the patient was observed to be icteric. The urine contained no bile pigment or bile salts. The oxalate plasma was icteric (1 to 60). The dialysate from the plasma contained no bilirubin or bile salts.

Another patient, a woman, who had always been in good health until an abortion was induced, which caused a streptococcus infection resulting fatally in ten days, entered the hospital with profound jaundice. On the day the plasma was examined the urine contained neither bilirubin or bile salts. The plasma was deeply jaundiced (1 to 275); Gmelin's test was very strongly positive. The aqueous dialysate contained neither bilirubin nor bile salts. The dialysate from alcohol and water contained bilirubin but no bile salts.

A man suffering from syphilitic myocarditis attended with general anasarca developed erysipelas on both thighs, where he violently scratched the skin with his finger nails. Within a few days after the onset of the erysipelas, the patient became icteric. The urine contained an abundance of bilirubin and no bile salts. The plasma was deeply stained (1 to 175). Gmelin's test was positive. The dialysate from the plasma (aqueous) contained bilirubin, but no bile salts.

The following case illustrates the behavior of bilirubinemia when the bilirubin is hemolytic in origin, but develops extravascularly.

A young man in perfect health received a stab wound of the left thorax four days prior to his admission to the medical ward of the hospital. A large amount of blood was found in the left pleural cavity, and 500 c.c. of the unclotted blood were withdrawn by paracentesis. The blood when centrifuged yielded only about 10 per cent. of its bulk in plasma. The blood did not clot on standing or after the addition of calcium. The plasma contained a small amount of oxyhemaglobin and a very large amount of bilirubin, and was not turbid. The bilirubin concentration was 1 to 450. Gmelin's test, also Huppert's and Hammarsten's test for bilirubin were strongly positive. The water dialysate from this plasma contained neither bilirubin, bile salts nor urobilin. The water and alcohol dialysate contained bilirubin, but no bile salts or urobilin. Blood from the patient's veins contained no bile pigment or bile salts and the urine contained no biliary elements.

This is a very striking instance of the adsorption of bile pigment in plasma. The concentration of bilirubin was much higher in the thoracic plasma than we have found in endovascular plasma in jaundice of any kind, and in spite of the very great accumulation of bile pigment in the intrapleural plasma no bilirubin was yielded to the collodion

dialyzer when water surrounded the sack. Some unknown change in the plasma occurs, to heighten its adsorptive power for bile pigment when blood escapes into a serous cavity in a healthy person.

In another patient who acquired a blood-serous exudate in the left pleural cavity on account of carcinoma of the pleura we found the same conditions of jaundice of the intrapleural plasma existed as in the case of traumatic hemathorax.

In none of our cases of obstructive jaundice did we find such a great disparity between pigmental cholemia and pigmental choluria as in our cases of hemolytic jaundice. When we speak of the threshold at which a concentration of bile pigment in the plasma will result in bile pigment appearing in the urine, however, it seems to us an error to regard this threshold as assignable to resistance offered by the renal filter to the passage of pigment. There is a wide variation of this so-called threshold, which can not be accounted for by varying renal function. The source of this threshold lies in varying adsorptive power of the plasma for bilirubin. On this basis we can account for the disparities which exist between the cholemia and choluria, and also for the varying disparities (in some patients) between the concentration of bilirubin in the blood and serous transudates, and the varying disparities between the jaundice of plasma and jaundice of the subarachnoid fluid; and finally for the varying threshold concentrations of bilirubin in the plasma toward the collodion dialyzer.

HEPATITIS

Hepatic dissociation jaundice in its relation to hepatitis is not clearly depicted in our experience. What constitutes hepatitis in many cases of acute infectious disease is not clear and should there be only bile pigment in the plasma and urine without bile salts, the question to solve is are we dealing with a dissociated pigmental jaundice of hepatic origin, or are we dealing with a hemolytic jaundice which is the result of the general infection? In other words, we are dealing with evidences of blood or liver deterioration as a result of infection. The question presents itself to us in this form, because thus far we have met with no instance of bile salts dissociation in the plasma of patients suffering from sepsis of any kind, or in patients with subacute or parenchymatous degeneration of the liver.

In two cases of pneumonia with jaundice we found only bile pigment in the plasma and no bile salts in either the plasma or urine. So there seemed very good reason for regarding the jaundice as hematogenous and not hepatogenous.

In two cases of acute infection we found large amounts of urobilin in the plasma along with bilirubin and bile salts. Great parenchymatous degeneration of the liver was proved in one of these cases at

necropsy and the other patient recovered after surgical drainage of a perigastric area of infection, which was due to a perforating ulcer at the pylorus.

In two cases of subacute hepatitis occurring in association with chronic interstitial hepatitis we were able to definitely ascribe the jaundice to a subacute hepatitis, and the plasma and urine both contained bilirubin and bile salts. In one case of chronic interstitial hepatitis, however, in which alcoholism and syphilis shared as etiological factors, the patient had an acute enlargement of the liver associated with jaundice. The patient was in the hospital three weeks. When he entered his plasma was icteric (1 to 100) and yielded bilirubin, but no bile salts, to the dialysate. The urine also contained bilirubin and much urobilin; bile salts were absent, and the stools contained an abundance of stercobilin. After a lapse of three weeks, during which time the jaundice diminished and all the other symptoms improved, the plasma was slightly icteric and gave bilirubin in the dialysate to alcohol and water, but no bile salts. The urine contained no bilirubin, bile salts or urobilin. These findings we must accept as a case of dissociated pigment jaundice of hepatic origin for the following reasons:

There was a moderate jaundice (1 to 100) and pigment was liberated through the renal filter and no salts were present in either the plasma or urine. Had there been complete biliary retention in the blood from a hepatic source, both the urine and the plasma dialysate would have contained bile salts or the urine would have contained bile salts before it would have contained bilirubin. This doubt may, however, be injected into the dissociation idea, namely, that the patient had complete jaundice before entering the hospital and renal dissociation of the bile salts may have been accomplished before he came under observation, as we saw him only during a period in which the pigment was a survival of complete jaundice. That we were not dealing with hemolytic jaundice is supported by the presence of a large amount of urobilin in the urine and the fact that bilirubin was excreted in the urine when there was only moderate icterus of the plasma. That we were not dealing with a residue from obstructive jaundice is attested by the abundance of urobilin in the urine and the abundance of stercobilin in the stools.

With the exception of this last case, we have not yet seen an instance in which we could seriously consider a dissociated pigmental jaundice of hepatic origin as a probability.

DISSOCIATED BILE SALTS JAUNDICE OF HEPATIC ORIGIN

Primary anemia affords some of the most striking characteristics of biliary elements in the blood. Of fourteen cases of primary anemia in which the plasma, urine and stools were examined for bile elements,

all but two showed bilirubin in the plasma and bile salts were present in large amounts in the dialysate from the plasma in both these cases. In none of the fourteen cases were either bilirubin or bile salts found in the urine.

In primary anemia we have seen the highest concentration of bilirubin in the plasma (without perceptible icterus of the skin or sclerae) which have come under our observation. It seems in primary anemia the fixation of bilirubin in the plasma is so firm that pigment is not only never yielded to the renal filter, but in some instances pigment is not yielded to the tissues when the plasma has a concentration of bilirubin as high as 1 to 150.

Of these two cases of bile salts dissociation, one, a man 52 years old, gave a history of having been ill for fourteen months. A few months prior to entering the hospital he had a marked lemon yellow color to his skin. On entrance there was no trace of icterus. Blood examination showed red blood cells, 2,312,000; white blood cells, 7,700; hemoglobin 70 per cent.; color index 1.5. A differential count gave polymorphonuclears, 67 per cent.; small mononuclears, 23 per cent.; large mononuclears, 7 per cent.; and transitionals, 3 per cent. The neurologic signs were very marked. There was a loss of both patellar and ankle reflexes, impairment of the vibratory sense in upper and lower extremities, and acroataxia and proximoataxia in both upper and lower extremities. The plasma was colorless and the plasma dialysate gave a reaction to Pettenkofer's test, which was strongly positive. The dialysate not only changed from cherry red to purple on standing twelve hours, but the spectroscopic examination showed that the movement of the absorption band on standing was from the purple into the orange. This was an instance of primary anemia. The patient formerly had pigment as well as salts in his blood, but during the period he was under our observation his blood contained an abundance of bile salts without pigment.

As to the other case of primary anemia which yielded salts from the plasma without pigment, there may be some doubt about the primary anemia. The diagnosis of primary anemia was made from the history of former anemia and the characteristic neurologic signs associated with degeneration of the posterior and lateral columns of the cord, with a normal cell count and negative Wassermann reaction on the spinal fluid. We regarded this patient as one who had recovered from his anemia with persistence of the neurologic symptoms. However this may be, the point of interest in this patient lay in the fact that bile salts were present in abundance in his plasma, as shown from the Pettenkofer test, with spectroscopic confirmation, and no bile pigment was found in the plasma or in the urine and no bile salts were found in the urine.

Two other cases of bile salts dissociation in the plasma were found in two cases of lead poisoning. Both patients had the characteristic lead line on the gums and both patients were exposed to lead poisoning. One was a house painter and the other worked in a storage battery factory. Neither patient had an anemia below 4,500,000 red cells and there was no icterus of the skin; neither was there any bile pigment or bile salts in the urine. The plasma in both cases was colorless, but the dialysate from the plasma in both cases gave a marked Pettenkofer reaction, which was confirmed by the change from a pink to a purple color, and the spectroscopic absorption band after twelve hours moved from the purple into the orange.

SUMMARY

1. We have found true dissociated jaundice of hepatic origin in two cases of primary anemia and in two cases of lead poisoning. In the four cases bile salts were found in the blood in large amounts, that is, the qualitative test for bile salts in the plasma dialysate was quite as strong as we find it in complete jaundice of pronounced severity.

2. Excepting in jaundice of hemolytic origin and in complete jaundice which has undergone renal dissociation, we have never found bile pigment without bile salts in the plasma.

3. Bilirubin and bile salts may both be present in very marked concentration in the plasma and neither pigment nor salts appear in the urine.

4. Adsorption of bilirubin in the plasma may not only withhold the pigment from the renal filter, but also from the tissues; so there may be pronounced cholemia (pigmental) without choluria (pigmental) and also without icterus of the tissues.

5. When pigmental cholemia is present (in varying degrees) without choluria, the collodion sack will yield no pigment to an aqueous dialysate from the plasma. When choluria attends cholemia (pigmental), the collodion sack will yield bile pigment to an aqueous dialysate from the plasma.

6. Bile salts will dialyze from plasma when no bile salts are demonstrable in the urine.

7. Without an examination of the plasma we are never justified in assuming that biliary elements have not been retained in the blood.

A COMPARISON, IN VARIOUS DISEASES, OF THE CARBON DIOXID TENSION IN THE ALVEOLAR AIR (PLESCH METHOD) WITH THE AMOUNT OF CARBON DIOXID IN THE VENOUS BLOOD (VAN SLYKE'S METHOD)*

I. CHANDLER WALKER, M.D.
AND
CHANNING FROTHINGHAM, Jr., M.D.
BOSTON

With the increasing interest among clinicians in regard to the amount of carbon dioxid in the blood and its relation to problems in respiration and acidosis, it is important, for the estimation of the carbon dioxid, to have methods which are applicable to most diseases and which may be frequently used in the same case.

Although previous to 1905 occasional observations had been made on the carbon dioxid content of the blood in animals and in man, by examination of the blood directly, a marked stimulus was given to this study on the introduction in 1905 by Haldane and Priestley[1] of a method for determining the content of carbon dioxid in the alveolar air. It is well recognized that the carbon dioxid tension in alveolar air corresponds closely to that of the blood in the arterial system.

Since 1905 different methods of collecting and studying the alveolar air have been devised by various workers. The results obtained by the different methods give slightly different figures. With some methods the carbon dioxid tension in the alveolar air corresponds to that in the venous blood, with others to that in the arterial blood. In 1914 Boothby and Peabody[2] compared the different methods of obtaining alveolar air from untrained subjects, and reached the conclusions that the Plesch[3] method as modified by Higgins[4] and slightly by themselves gave very constant results. This method depends on the ready diffusibility of carbon dioxid, so that after rebreathing a limited amount of air in the

* Submitted for publication May 27, 1916.
* From the Medical Clinic of the Peter Bent Brigham Hospital.
* A portion of this work was made possible through a gift to the Peter Bent Brigham Hospital, by Mr. Charles F. Choate, Jr., for the study of Bronchial Asthma.

1. Haldane and Priestley: Jour. Physiol., 1905, xxxii, 225.
2. Boothby and Peabody: The Archives Int. Med., 1914, xiii, 497.
3. Plesch: Ztschr. f. Exper. Pathol. u. Therap., 1909, iii, 380.
4. Higgins: Publication No. 203, Carnegie Institution of Washington, 1915, p. 168.

closed system for a certain time the carbon dioxid tension is uniform throughout the closed system. Therefore the carbon dioxid tension in the air in the collecting bag is the same as that in the alveoli. This in turn is the same as that in the venous blood, since there is no opportunity for the escape of carbon dioxid. Of course, in this test the time allowed for breathing into the closed system is important, in order to avoid a heaping up of carbon dioxid above what was in the venous blood at the start of the rebreathing.

Boothby and Peabody tried out this method in a variety of diseases, and on patients who could not always cooperate with them. Nevertheless they obtained very consistent results. One of us during this past winter has been working with this method of determining the carbon dioxid tension in the alveolar air in a variety of different diseases. In many of these cases the respiratory rate was elevated. In others the patients were unable to cooperate in the technic advised for the collection of the air sample. It seemed desirable therefore to check up these results with the determinations obtained by a direct study of the venous blood for its carbon dioxid content. Such an opportunity was offered by the method recently devised by Van Slyke[5] for the study of the carbon dioxid tension in blood taken directly from the vein.

This study has consisted therefore in a comparison of the results obtained from the determination of the carbon dioxid tension in the alveolar air and the estimation of the carbon dioxid tension in the venous blood as figured from a determination of the total carbonates in this blood. For the former the Plesch-Higgins method was used and for the latter that devised by Van Slyke. The studies were carried out on a variety of diseases, in which various degrees of severity were represented. The specimens of both air and blood were collected at approximately the same time, two or more hours after eating. If any slight interval did occur between the collection of the air and blood, care was taken to see that the patients did not receive any food or fluid in the interim.

The air was collected in the apparatus as described in detail by Boothby and Peabody.[2] The rubber bag was filled with 1,000 c.c. of air before the breathing began. Although it was impossible in many cases to adhere even closely to the prescribed five breaths in the twenty-five seconds allowed for breathing into the closed system, care was taken in all cases to preserve the exact limit of time. In all cases, except those in which the breathing was quite deep, effort was made to have the patient increase slightly the depth of the respirations. From each patient three separate samples were collected each time and

5. Van Slyke: Jour. Biol. Chem., 1916, in press.
6. Haldane: Methods of Air Analysis, London, Charles Griffin & Co., Ltd., 1912.

then analyzed by the Haldane[6] method for gas analysis. Usually these three samples varied from each other less than 2 mm. of tension, and an average of the three was taken. Occasionally one of the three showed considerable variation, in which case the one that showed the variation was left out of the reckoning. If one differed considerably it always showed an extra low tension, and presumably was due to some slip in the technic in obtaining the sample.

The blood for the Van Slyke test is drawn directly from a vein into enough potassium oxalate to make 1 per cent. or less of the amount of blood. It is then immediately centrifugalized and the plasma pipetted off, so that not more than fifteen minutes elapsed between the withdrawal of the blood and the analysis of the plasma. It is felt that this time is too short to make any appreciable difference in the alkaline content of the plasma. The plasma is then saturated with carbon dioxid at a known tension. One of us (Walker) modified slightly Van Slyke's technic at this point so that the plasma is saturated as follows: A separatory funnel of 250 c.c. capacity is filled from a spirometer with air of a known carbon dioxid percentage. Into this funnel 3 c.c. of the plasma is placed and shaken for two minutes. One c.c. of this saturated plasma is then immediately examined for its carbon dioxid content by the method described by Van Slyke.[5] The figure obtained after being corrected for temperature and barometric pressure represents the number of milligrams of carbon dioxid in 1 c.c. of plasma. Van Slyke found that multiplying this figure by the constant 35 gives a figure comparable to that obtained for the carbon dioxid tension in the alveolar air.

The air used in saturating the plasma varied in this work in carbon dioxid content from 5.1 to 6 per cent., with an average of 5.8 per cent. in most cases. Comparative studies showed that the final results varied slightly with variations in the carbon dioxid percentage used for saturating the plasma. The amount of variations, however, with these extremes of carbon dioxid percentage was too small to make any practical difference. It seemed, however, that this method for saturating the plasma would be less subject to fluctuations in the carbon dioxid percentage of the saturating air than would be obtained by blowing through the separator, as recommended by Van Slyke. At first the blood determinations were made in duplicate from the same sample, but the results were so consistent that in our later work control determinations were made only when unexpected results were met, and in all cases these were found to agree with the originals.

The observations are grouped by diseases and recorded in tables. Each observation does not represent an individual case, because on a few of the cases more than one study was made. A total of 116 obser-

vations were made on 100 different cases which represented thirty types of disease. As a rule, cases were chosen in which there was not a complication of diseases.

TABLE 1.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Primary Anemia

Number	Carbon Dioxid Tension, Mm. Air	V. Blood
3538	39.7	37.7
3690	39.3	40.6
3863	36.7	34.8
4063	42.5	45.5
4064	38.6	40.6
4223	46.2	45.8

In the group of cases of primary anemia shown in Table 1 the carbon dioxid tension in the air varied in different cases by about 10 mm. The relation, however, between the results of the air and the blood studies was very close in each case, and the greatest difference was only 3 points. When a variation did occur, in some cases, the carbon dioxid tension in the air was slightly higher and in others it was slightly lower than that in the blood.

TABLE 2.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Graves' Disease

Number	Carbon Dioxid Tension, Mm. Air	V. Blood
3434	54.4	43
3591	46	40
3792	43.5	40.2
3748	45.4	45.2
3989	41.2	40
4040	40.9	36.1
4075	40.6	39
4311	43.9	40.6

In the group of cases of Graves' disease represented in Table 2 the carbon dioxid tension in the alveolar air was always slightly higher than that in the blood, and in a few of them this difference was considerable. In the first case with the exceptionally high tension in the alveolar air repeated estimations gave the same result. Just what causes this elevation of the tension in the air in comparison to that in the blood is not clear. It may bear some relation to the fact that the patient's metabolism was about 75 per cent. above normal at this time.

TABLE 3.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Typhoid Fever

Number	Carbon Dioxid Tension, Mm. Air	V. Blood
3522	41.8	41.5
3601	32.3	36
3601	38.6	37.5
3601	45.6	42.3

The last two observations in Table 3 were made after the patient was free from fever. In these two cases of this disease the relation between the two tests is close; neither one was consistently elevated above the other.

TABLE 4.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Lung Abscess

Number	Carbon Dioxid Tension, Mm. Air	V. Blood
3834	40.3	41.3
4226	41.2	40.2
4149	41.5	38.8

In the small group of cases of lung abscess represented in Table 4 the results from the two tests correspond very well.

TABLE 5.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Chronic Nephritis

Number	Carbon Dioxid Tension, Mm. Air	V. Blood
3507	44	41.5
3520	38.7	37
3369	40.1	36.7
3644	27.9	28
3821	18.2	13.3
3990	39.5	37.8
4253	29.9	32.9

The group of cases summarized in Table 5 is of special interest because it includes some cases of chronic nephritis which showed a marked lowering of the carbon dioxid tension in the alveolar air. The same close relation still exists between the results obtained from the air and the blood studies throughout this group. In some cases the figures for the air tension are slightly higher, in others slightly lower than the figures for the blood.

TABLE 6.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Syphilis

Number	Carbon Dioxid Tension, Mm. Air	V. Blood
3857	44.2	44
3857	44.3	43.1
4143	43.2	39.2

The three observations shown in Table 6 made on two cases of syphilis in the stages of a fading general eruption agree closely.

TABLE 7.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Chronic Cardiac Disease

Number	Carbon Dioxid Tension, Mm. Air	V. Blood
3539	46.4	38.5
3632	39.1	41.6
3730	43.2	40.9
3460	40.2	38.1
4036	46.3	48.0

The cardiac cases represented in Table 7 were not acutely decompensated at the time, although the patients had to be upright in bed and became dyspneic on slight exertion. Except for the first one in the table, the variation in the results between the blood and air studies is slight. No explanation is offered for this variation. It may be added that this first patient had considerable emphysema.

TABLE 8.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Pneumonia

	Carbon Dioxid Tension, Mm.	
Number	Air	V. Blood
3608	37.9	37.1
3630	40.3	34.6
3630	33.8	33.6
3642	34.5	35.7
3677	44.2	47.6
3699	45.9	40.6
3699	47.6	49.0
3825	37.6	37.4
3813	28.5	34.3
3853	37.5	30.5
3883	34.2	30.8
3883	44.7	41
3882	34.7	34.8
3882	41.9	41.6
3885	42	40.3
3944	38.1	41
3965	41.6	42.7
4046	45.1	38.8
4046	45.1	42
4044	33.4	36.1
4053	42.4	38.8
4053	41.5	41.3
4263	36.3	45.5
4263	44	42.3
4280	43.1	38.8
4237	38.8	42

The twenty-six observations on nineteen different cases of pneumonia shown in Table 8 were especially interesting because in the majority of them the respirations were rapid. In many the patients were too ill to cooperate intelligently in the collection of the samples of air. In the cases in which two observations were made, the second was made after the temperature had returned to normal. The group showed variations in the carbon dioxid tension in the alveolar air covering a range of 14 mm.

In the majority of these cases, even in those studied under unfavorable conditions, the results of the blood and air examinations agree very well. In Nos. 3630 and 4263, however, the results from the two tests show a considerable variation, which is also misleading, for in one case the figures for the alveolar carbon dioxid tension are normal, while the blood study suggests an acidosis, while in the other case the reverse is true. No explanation is offered for these variations.

TABLE 9.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Acute Articular Rheumatism

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3715	33.2	35.3
3715	41.0	37.8
3712	37.1	35.7
3712	35.8	36.7
3712	36.6	37
3712	39.8	38.2
3662	35	35.2
3662	31.2	32.5
4088	33.2	37.1
4371	38.2	41
4417	44.5	39.5
4534	43.3	43.7

In the twelve observations on seven cases of acute articular rheumatism represented in Table 9 the comparison between the results is very close although the carbon dioxid tension varied over a range of thirteen points. In some of the cases in which there was a slight difference between the figures for the blood and air, the figure for the air was higher and in others it was lower than that for blood.

TABLE 10.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Diabetes

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3738	34.7	30.8
3746	36.6	34
3757	34.6	27.6
3880	32.3	31.2
4008	40.8	41.6
3988	35.5	33.6

In five of the six cases of diabetes shown in Table 10 the air and blood show practically the same carbon dioxid tension. The sixth one shows a more marked variation, yet both determinations showed evidence of an acidosis, so that the variation in this case would not be especially misleading. It is interesting to note that in all the cases of this group which showed acidosis the blood was lower in carbon dioxid than the air.

TABLE 11.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Gastric Cancer

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
4336	39.2	38.4
3799	37.4	40.6

In the two cases of gastric cancer represented in Table 11 the results are quite similar.

TABLE 12.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Cirrhosis of the Liver

	Carbon Dioxid Tension, Mm.	
Number	Air	V. Blood
4007	43.7	41.7
4170	38.2	38.1

These two cases of cirrhosis of the liver summarized in Table 12 showed a very close relation between the tests.

TABLE 13.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Acute Nephritis

	Carbon Dioxid Tension, Mm.	
Number	Air	V. Blood
3780	27.4	31.2
4160	39.5	40.6
4273	40.3	36.7
4245	46.2	45.5
4314	48.5	48
4380	18.7	15.7

The group of six cases of acute nephritis shown in Table 13 included both mild and severe types, and therefore the variation in carbon dioxid tension in the air varied from above normal to very low. It is interesting to note how closely the air and blood determinations agree in all the cases of this group, in which such marked variations in the carbon dioxid tension occur.

TABLE 14.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Asthma

	Carbon Dioxid Tension, Mm.	
Number	Air	V. Blood
3529	31	37.5
3529	33.6	37
3582	40	37.5
3856	43.3	37.9
3683	40	38.5
3934	39.3	38.5
4161	44.3	42.7
4467	41.8	38.2
4507	37.7	37.8
4563	36	38

Cases 3529 and 4563 in Table 14 were studied during the end of an asthmatic attack and showed the carbon dioxid tension in the air below that in the blood. The figure obtained from the blood examination is presumably the correct one, as difficulty in collecting a proper sample of air during an asthmatic attack has been found by one of us (Walker). In the cases studied between attacks the results from the air and blood determinations agreed very well. Usually the figures for the air estimations were slightly higher than those for the blood.

TABLE 15.—Carbon Dioxid Tension in Alveolar Air and in Venous Blood in Miscellaneous Diseases

Number	Diagnosis	Carbon Dioxid Tension, Mm. Air	V. Blood
3559	Tumor rt. kidney	42.2	39.2
3566	Acute endocarditis	41.7	39.5
3787	Acute bronchitis	41.9	39.9
4359	Polycythemia	46.7	46.2
3905	Gonococcus arthritis	39.7	38.5
4254	Tuberculosis	39.7	39.5
3942	Tonsillitis	39.9	36
3955	Perirenal abscess	41.9	40.6
4025	Typhus	45.9	39.2
4031	Erythema nodosum	43.5	41.5
4120	Bronchopneumonia	30	36
4166	Gout	45.9	43.7
4180	Lymphatic leukemia	38.3	43
3281	Portal thrombosis	38.5	37.1
4197	Myxedema and chr. nephritis	38.3	40.2
4299	Addison's disease	38.7	37.1

In the group of sixteen cases shown in Table 15 the carbon dioxid tension in the alveolar air is very similar to the estimated carbon dioxid tension in the venous blood, except in two cases. In each of these cases a difference of six points occurred for which no explanation is available.

In summing up these 116 observations it appears that in the great majority of these cases the carbon dioxid tension in the alveolar air, as collected by the Plesch method, corresponds with that as estimated in the venous blood by Van Slyke's method. Exceptions were met in Graves' disease, pneumonia, and asthma, but even in these diseases, except during an attack of asthma, the variations occurred in only a very small percentage of the cases.

In most of these cases the alveolar air was collected for the first time. In many, especially the febrile cases, the patients were unable to cooperate in the collection of the air sample. It is interesting to note that subsequent studies on several of the cases in which marked differences occurred on the first examination showed practically identical results in the air and blood studies.

From these observations it seems fair to conclude that the carbon dioxid tension in the alveolar air, as determined by the Plesch-Higgins method, agrees very closely with the results obtained by the Van Slyke method of determining the amount of carbon dioxid in the venous blood and is therefore a very accurate index of the amount of carbon dioxid in the venous blood. Furthermore, this method is applicable to a great variety of acute and chronic diseases.

We are indebted to Miss Barker, the laboratory assistant, for estimating the carbon dioxid tension in the samples of alveolar air.

Peter Bent Brigham Hospital.

CHRONIC INFLUENZA IN PULMONARY TUBERCULOSIS *

MARY L. HAMBLET, M.D., AND HARRY LEE BARNES, M.D.
WALLUM LAKE, R. I.

It has been our object to obtain data as to the frequency of influenza infection as a complication of phthisis; as to the frequency with which the symptoms of patients diagnosed as having pulmonary tuberculosis, but with negative sputum, may be accounted for by chronic influenza infection, and as to what extent the percentage of recoveries in sanatoriums for tuberculosis have been swelled by the inclusion of cases of influenzal bronchitis.

Influenza bacilli are said to be present in a large percentage of the population.[1] Lockhardt's[2] summary of the results of Scheller, Holt, Lord, Davis, Allen, Boggs, Grassberger and Wollstein shows that in 172 supposedly normal persons, organisms of the influenza type were found in 25 per cent., while in 427 cases of infection they were found in 50 per cent. Leutscher[3] found the influenza bacillus responsible for 22 per cent. of 388 cases of acute infection of the respiratory tract. Hastings and Niles[4] found influenza bacilli in only 1.5 per cent. of cases of infection of the respiratory tract. Webb[5] has reported fifteen tuberculous patients who succumbed to epidemic infection with the influenza bacillus. Koch[6] stated that when influenza is prevalent "cases occur which, to the eye of the clinical observer, exactly resemble incipient tuberculosis, but are not that." Madison[7] reported six cases of chronic influenzal bronchitis which had much clinical similarity to tuberculosis.

Lord's[8] work is of special interest. In 1902 he found influenza bacilli present in the sputum of sixty out of 100 patients with cough, presenting themselves at the Massachusetts General Hospital, and with no evidence of tubercle bacilli in the sputum. In 1905 Lord[9] reported on 186 cases similarly studied. In 59 per cent. of these "organisms having the morphology and staining reactions of influenza bacilli were seen in varying numbers. In 30 per cent. the organisms

* Submitted for publication May 12, 1916.

1. Cabot, R. C.: Differential Diagnosis, Ed. 2, 1913, i, 467.
2. Lockhart: Ann. of Otol., Rhinol. and Laryngol., 1914, xxiii, 327.
3. Leutscher: THE ARCHIVES INT. MED., 1915, xvi, 657.
4. Hastings and Niles: Jour. Exper. Med., 1911, xiii, 646.
5. Webb: Kleb's Tuberculosis, p. 590.
6. Koch: British Congress on Tuberculosis, iii, 94.
7. Madison: Jour. Am. Med. Assn., 1910, lv, 477.
8. Lord: Boston Med. and Surg. Jour., 1902, cxlvii, 659.
9. Lord: Boston Med. and Surg. Jour., 1905, cliii, 537.

were shown by culture to conform in all respects to the cause of epidemic influenza." Four of Lord's patients had been admitted to consumptive homes.

The clinical material for this investigation consisted of 320 patients of the Rhode Island State Sanatorium. Two hundred and twenty consecutive patients having negative sputum were examined in the years 1912 to 1915, and 100 patients with positive sputum were examined in the winter and spring of 1916.

The diagnosis of pulmonary tuberculosis in 200 cases having negative sputum was made on the history, symptoms and physical signs. There was a family history of tuberculosis in 36 per cent., a history of pleuritic pain in 55 per cent., of hemoptysis in 45 per cent., of fever in 51 per cent., of night sweats in 46 per cent., and tubercle bacilli were found subsequently in 15 per cent. In thirty-two cases it was thought advisable to test with tuberculin subcutaneously and the result was positive in all. Twenty patients whose sputum was negative for tubercle bacilli and influenza bacilli, cultures having been made for the latter in thirteen cases, were excluded from the above series because the diagnosis of tuberculosis was considered doubtful.

In 50 cases of the first series the cultures were made by Dr. Mary E. Gaffney, all the remaining cultures were made by Dr. Hamblet.

The technic was as follows: The patients were required to deposit in bottles which had been boiled only morning sputum actually raised. In the first 100 cases the technic of Lord was used, with slight variations in the method of washing the particles of sputum selected for inoculation. In the first forty-three cases sterile bouillon or normal salt solution was employed, two washings being made. In the succeeding fifty-seven cases Armstrong's[10] method of washing the sputum in tap water was followed. The culture medium in all three series was agar, the surface of which had been smeared with a few drops of human blood under aseptic precautions. Of the cultures made from the first 100 cases, ninety-three failed to show any influenza-like organisms. Of the seven suspicious cases, three were proved negative to influenza by subcultures, three remained doubtful and in only one was the influenza bacillus positively identified.

In the second series of 100 cases cultures were made only in those cases in which the stained smears from the sputum showed gram-negative rods having some similarity to the influenza bacillus. The technic of Park & Williams[11] was followed in this series, the chief

10. Armstrong: Lancet, London, 1912, i, 1339.
11. Park and Williams: Pathogenic Micro-Organisms, Ed. 4, 1910, p. 358.

point of difference being that the sputum was not washed before inoculating blood agar plates. In accordance with a recommendation from the New York City department of health laboratories, we used in this series agar having a reaction neutral to phenolphthalein. In the other two series the reaction of the agar was acid to phenolphthalein (+1). Cultures were made in twenty cases of the second series, and in six of these micro-organisms having the characteristics of the influenza bacillus were found to be present.

In the third series, for purposes of comparison, a study was made during the spring of 1916 of the sputum in 100 cases which had previously shown tubercle bacilli in the sputum. Sputum for this series was collected in paper sputum cups. Smears stained by the Gram-Weigert method were examined and cultures made by the method of Park and Williams in all suspicious cases. The smears from twenty-three cases showed bacilli having some resemblance to the influenza bacillus. In seven of these the micro-organisms were proved to have the characteristics of the influenza bacillus.

Of the fourteen patients whose sputum contained influenza bacilli, there had been a clinical history of influenza in but three.

The cases in the first two series were examined uniformly at all seasons of the year. Six of the seven sputums from which the influenza bacillus was recovered were examined during the winter and spring months.

From the second and third series of the writers' work it appears that bacilli having the morphological and cultural characteristics of influenza bacilli were recovered from the sputum of 6 per cent. of our sanatorium patients having negative sputum and from 7 per cent. of patients having positive sputum. As these bacilli were never in pure culture or even predominating over other organisms, it does not seem probable that they constituted a serious complication in those having positive sputum or that they were the real cause of lung disease in those having negative sputum. It is perhaps not impossible that a true influenza infection of the lung may have originally been present in some of these cases and that the infection may have so improved that the influenza bacilli ceased to predominate before the patients were admitted to the sanatorium. If it should be granted, however, that all patients in the above series whose sputum was positive for influenza and negative for tubercle bacilli had influenzal bronchitis and were free from active tuberculosis, this would amount to but 6 per cent. of cases having negative sputum and only about 2 per cent. of all patients discharged from the sanatorium. This percentage would be too small sensibly to affect the accuracy of our sanatorium statistics.

SUMMARY

1. Of 100 patients in series 1, diagnosed as having closed tuberculosis whose sputa were cultured for influenza, at least ninety-six were negative.

2. Of 100 patients in Series 2, diagnosed as having closed tuberculosis, influenza bacilli were recovered from six.

3. Of 100 patients in Series 3, with open tuberculosis, influenza bacilli were recovered from seven.

4. Of twenty patients in whom the diagnosis of tuberculosis continued doubtful, the sputum was negative for influenza bacilli in all.

5. In none of the patients examined did the influenza bacilli occur in pure culture nor were they the predominating organism.

CONCLUSION

A study of 320 sanatorium patients, extending over four years, furnished no evidence that influenzal bronchitis frequently simulates or complicates pulmonary tuberculosis.

STUDIES IN BLOOD PRESSURE

WITH ESPECIAL REFERENCE TO DIASTOLIC AND PULSE PRESSURE READINGS *

WILLIAM W. CADBURY, M.D.
BOSTON

Hypertension is a well-recognized pathologic sign, but the discrimination of varying degrees of high blood pressure is often considered of little value to the diagnostician, and although the diastolic pressure is generally recorded, both it and the pulse pressure are often neglected in making diagnoses and prognoses. The purpose of the present paper has been, therefore, to emphasize especially the valuable data to be obtained from diastolic and pulse pressure readings.

MATERIAL EMPLOYED

The material consists of the hospital records of 305 patients who entered the medical service of the Peter Bent Brigham Hospital during the years 1913, 1914 and 1915. These 305 patients are selected from the first 3,000 admissions to the wards, being all of those who had at least one reading of systolic pressure of 160 mm. of mercury, or more, and in whom at least two tests of the pressure were made. Since it is customary to make two or more tests of the blood pressure in all medical cases showing hypertension or hypotension, and since at least one test is made of every patient admitted, we have here very nearly all the cases of hypertension seen in the medical service during these three years. The Faught mercury manometer instrument was used in this work and the readings were made by the auscultatory method.

All the clinical records in the hospital are made with the greatest care and are frequently checked up. The physical examination of the heart was usually checked up by three or four different physicians, and electrocardiography and Roentgen ray were called into service whenever any doubt existed as to the nature of the cardiac lesion or the presence of enlargement. The diagnosis was verified by necropsy in thirty-one cases. The presence of arteriosclerosis was determined by palpation of the vessel walls (radial and other arteries) and by ophthalmoscopic examination of the retinal vessels.

The maximum and minimum systolic, diastolic and pulse pressure readings were put down and an average taken from these. A few of

* Submitted for publication May 1, 1916.
* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

the nephritic cases, in which necropsies were performed, have already been reported by Frothingham.[1]

A comparison of the findings in the present study with those of Janeway,[2] is instructive. The series of cases reported by Janeway consisted of private patients. Only those showing a systolic blood pressure of over 160 mm. of mercury were classified by him as hypertension cases. Of a total of 7,872 patients examined, 11.1 per cent. showed at some time this degree of hypertension, a percentage very similar to that for our hospital patients. He fails to consider diastolic pressure at all. Very few necropsies were performed in this series, no functional renal tests were made, and the electrocardiograph and Roentgen ray were not used.

Of the 305 patients in our series, thirty-two were admitted twice, eighteen three times, four four times and three five times, thus making a total of 397 hospital admissions. A few patients were observed but two or three days, but the great majority remained in the hospital at least one week, and one was under treatment continually for 149 days. Several of the patients were observed from time to time for two years and longer.

The following is a complete list of the data recorded from each case for analysis: hospital number, number of days in the hospital at each visit, initials of name, sex, age, diagnosis, condition of the heart according to physical examination, electrocardiogram, Roentgen-ray examination of chest and postmortem findings; presence or absence of arteriosclerosis, condition of kidneys as suggested by albuminuria (largest amount recorded on any examination), phenolsulphonephthalein test (lowest reading recorded), blood urea nitrogen (highest recorded reading), postmortem findings of the kidney; cerebral symptoms as indicated by palsies, uremia, or convulsions; the Wassermann test; the result at final discharge from hospital. Under blood pressure were recorded the number of readings made, the maximum, the minimum and the average of systolic, diastolic and pulse pressure, together with the percentage heart load as estimated from average readings; the tendency of systolic, diastolic and pulse pressure to rise or fall; the influence of digitalis; time elapsing from first admission to last discharge; subsequent reports of patient's condition after leaving the hospital. These data were obtained from the hospital records and the original observations were made without any reference to utilization in a study of the sort that is here made.

1. Frothingham: Am. Jour. Med. Sc., 1916, cli, 72.
2. Janeway: THE ARCHIVES INT. MED., 1913, xii, 755.

SEX

In our series of patients 163 were male and 142 female. For the year 1914 there were 1,605 males and 1,238 females admitted to the medical and surgical services of the hospital, that is, about 56 per cent. of males and 44 per cent. of females. In our 305 cases 53 per cent. were males and 47 per cent. were females. Since, therefore, more males are admitted to the hospital than females, we may conclude that sex had little bearing in causing hypertension in our cases.

AGE

The Peter Bent Brigham Hospital has no children's ward and very few children are admitted. It will be observed from the table below that the majority of patients were between the ages of 40 and 70 years. In Janeway's[2] cases 80 or 90 per cent. of the patients were between the ages of 40 and 69 years, and the next largest percentage between 70 and 79 years. As he indicates, these ages are higher than hospital statistics would show. In the present series there were 68.52 per cent. between the ages of 40 and 69 years and the next largest group was found in the period of 30 to 39 years. The following tabulation shows the number of patients and the percentage, by decades as to age:

Age, Years	No.	Per Cent.	Age, Years	No.	Per Cent.
10 to 19	11	3.6	50 to 59	97	31.8
20 to 29	24	7.86	60 to 69	56	18.36
30 to 39	39	12.78	70 to 79	21	6.88
40 to 49	56	18.36	81	1	0.32

DIAGNOSES

	No.	Per Cent.
1. Chronic nephritis, with or without myocarditis, but without organic valvular disease	141	46.2
2. Chronic nephritis, associated with chronic valvular disease of the heart	27	8.9
3. Chronic nephritis, with or without myocarditis, complicated by disease other than of the circulatory system	54	17.7
4. Simple chronic myocarditis[3]	11	3.6
5. Chronic myocarditis with valvular disease	1	0.3
6. Chronic myocarditis with complications other than of circulatory or urinary systems	5	1.6
7. Simple valvular disease of the heart, angina pectoris and aortic disease without definite lesions of the kidneys or the myocardium	20	6.6
8. Other conditions	46	15.1

3. Chronic myocarditis is used throughout this paper in the sense of myocardial insufficiency arising from disturbance in the musculature, either functional or organic, in cases not associated with organic valvular lesions. Some of these showed at necropsy fatty degeneration of the myocardium as the only demonstrable lesion of the musculature.

A total of 72.8 per cent. of the patients suffered from chronic nephritis. A differentiation of parenchymatous and interstitial nephritis is not made, for cases that clinically showed all the signs of one variety at necropsy proved often to be the other. These diagnoses were made with considerable care after consideration of all the findings during the patients' stay in the hospital. They were not fixed until the patient was discharged.

Of other conditions, we find that arteriosclerosis was present in 186, or 60.98 per cent. of cases, and absent in 90, or 29 per cent. There were twenty-nine cases in which no record was made, but here the condition if present at all must have been very slight.

In 15.1 per cent. of the patients there was hypertension, without any apparent cardiac or renal disease. The primary conditions in these patients were carcinoma of the lung, prostate and stomach, with more or less metastasis; pulmonary emphysema, cirrhosis of the liver, amyotrophic lateral sclerosis, pernicious anemia, general arteriosclerosis, meningitis, dyspituitarism, cerebral arteriosclerosis, influenza, chronic morphin poisoning, chronic lead poisoning, taenia saginata, hyperthyroidism, syphilis, splanchnoptosis, cerebral hemorrhage, constipation, tabes dorsalis, acute gout, hemochromatosis, general miliary tuberculosis, tumor of the cerebellum, varicose ulcers of the leg, chronic malaria with hemorrhoids, mucous colitis and hemorrhoids, obesity, chronic arthritis, and papilloma of the bladder. Of course many of the above conditions were not the cause of hypertension, but their symptoms overshadowed any other obscure disease of the kidney, heart, etc. Undoubtedly there was, in some of these cases, a mild form of chronic nephritis.

A Wassermann test was made in 263 of the cases and in thirty-two, or about 12 per cent., the reaction was positive. Walker and Haller[4] in their report of routine Wassermann examinations of four thousand hospital patients at the Peter Bent Brigham Hospital found 120 cases of chronic nephritis with hypertension, and only seven of these gave a positive Wassermann reaction (about 5 per cent.), while among ninety-three cases of chronic nephritis without high blood pressure, three had a positive Wassermann reaction. In 1,700 successive medical patients in whom Wassermann reactions were done 12 per cent. had positive reactions, the same percentage as was found in these hypertension cases.

Many of the patients were already in an advanced state of disease when admitted to the hospital wards, and they are not to be compared with early cases of hypertension, such as one sees in private practice.

CASES SHOWING NO ALBUMINURIA

The urine was carefully tested for albumin in every one of the 305 cases reported in this paper, and as a rule an examination was made at least every week or ten days. In thirty-one of our patients no albu-

4. Walker and Haller: Jour. Am. Med. Assn., 1916, lxvi, 488.

min was found, although in eight but one test was made. Of these patients without albuminuria, in seven the high pressure was associated with dilatation of the arch of the aorta, syphilitic aortitis or aortic regurgitation; in five there was angina pectoris, chronic myocarditis or mitral regurgitation; in three there was cirrhosis of the liver with marked arteriosclerosis.[5] One patient with lead colic improved in symptoms during his eight days in the hospital, the pressure falling to nearly normal. Another patient had amyotrophic lateral sclerosis, associated with arteriosclerosis. There were four cases diagnosed as chronic nephritis, because of the hypertension and a left ventricular hypertrophy, although the urinary findings were negative. All of these cases showed definite arteriosclerosis, however. In one case the diagnosis was general arteriosclerosis.

Of the remaining nine cases without albuminuria four, diagnosed constipation, splanchnoptosis, cancer of the stomach and tabes dorsalis, showed more or less arteriosclerosis. This leaves in this group five patients with no apparent explanation for hypertension. These were chronic morphin poisoning, taenia saginata, general miliary tuberculosis, neurasthenia with tabes dorsalis and chronic malaria. In three of these the heart was slightly enlarged, and the maximum systolic pressure was under 165 in three.

It may be safely stated that albumin can be detected in the great majority of persons suffering from hypertension, if repeated examinations are made. When it is absent, one may look for some cardiovascular disease as the probable cause of the increased tension.

TABLE 1.—PHENOLSULPHONEPHTHALEIN EXCRETION AND SYSTOLIC AND DIASTOLIC PRESSURE

Phenolsulphonephthalein Reading, %	Number Cases	Average Systolic Pressure, Mm.	Average Diastolic Pressure, Mm.
0	29	196	117
1 to 10	15	194	119
11 to 20	25	180	108
21 to 30	33	192	112
31 to 40	43	185	112
41 to 50	40	177	106
51 to 60	39	178	77
61 to 70	14	169	94
71 to 80	6	158	89

5. One of these later proved to have chronic nephritis also.

The phenolsulphonephthalein test of renal function was made in 244 of the 305 patients. In many cases especially those with lower values several tests were made, in which case the minimum reading was selected. The average systolic and diastolic pressures in each case were taken and all averaged together. It is interesting to note the progressive fall in the pressure readings with the rise in the phenolsulphonephthalein readings. Of the thirty-one cases which showed no albuminuria, phenolsulphonephthalein was taken in fifteen. The lowest was 38 per cent. in two. In all the others it was over 40 per cent.

TABLE 2.—THE BLOOD UREA NITROGEN COMPARED WITH THE AVERAGE SYSTOLIC AND DIASTOLIC PRESSURES

Blood Urea N, Mg. per 100 C.c. Blood	Number Cases	Systolic Pressure, Mm.	Diastolic Pressure, Mm.
1 to 20	20	187	106
21 to 30	14	194	110
31 to 40	13	208	115
41 to 60	11	186	119
61 to 100	10	187	114
101 to 253	7	211	122

The blood urea nitrogen was examined in only seventy-five patients. Here again we may observe a gradual tendency to an increase in the average systolic and diastolic pressures. This is especially notable in the diastolic pressure, which shows a more consistent rise than the systolic. This may be due to the other complications influencing the systolic pressure as the intoxication became more profound and interference with cardiac function became more pronounced.

HEART LOAD

W. J. Stone[6] has contributed an interesting article on the importance of estimating the "heart load" as he calls it. This is determined by dividing the pulse pressure by the diastolic pressure (P.P./D.P.). Now taking 120 mm. as normal for systolic pressure and 80 mm. for diastolic pressure, we have the normal pulse pressure of 40 mm. This makes the normal ratio of pulse pressure to diastolic pressure 50 per cent. Stone finds in normal individuals a variation in heart load between 40 and 60 per cent. If the ratio exceeds this, according to Stone, we have to do with cardiac overload. Barach and Marks[7] state that according to their findings in normal individuals the pulse pressure equals from 20 to 80 per cent. of the diastolic pressure in 75 per cent. of cases. This wide

6. Stone, W. J.: Jour. Am. Med. Assn., 1913, lxi, 1256.
7. Barach and Marks: THE ARCHIVES INT. MED., 1914, xiii, 648.

variation would tend to vitiate the findings of Stone[8] in pathologic conditions in which he considers that this ratio is of considerable value in determining the functioning ability of the heart. Stone classifies seventy-five patients with circulatory disturbance into four groups, as follows: (1) hypertension (cerebral group); (2) hypertension (cardiac group); (3) myocardial and valvular lesions with increased heart load ratio; (4) myocardial and valvular lesions with decreased heart load ratio.

These groups he describes as follows: Group 1 showed a systolic pressure of about 202 mm., diastolic of 134 mm., and pulse pressure of 68 mm. The average heart load was 51 per cent.; that is, the heart showed compensatory ability in spite of a high diastolic pressure. In this group are found patients with hypertension, who die of uremia associated with chronic interstitial changes in the kidneys.

In Group 2 there was an average systolic pressure of 180 mm., diastolic pressure of 92 mm. and pulse pressure of 88 mm. The heart load averaged 96 per cent. The distinctive feature in these cases was the low diastolic pressure as contrasted with the high diastolic pressure of the former group. The urine was negative for albumin and casts in a large majority of these cases, and the heart was hypertrophied. There were symptoms of cardiac decompensation.

In Group 3 the systolic pressure averaged 112 mm., the diastolic 60 mm. and the pulse pressure 52 mm. There was a heart load of 86 per cent. In this group were cases of aortic incompetency and other valvular lesions of the heart.

Group 4 was made up of cases showing cardiac dilatation and myocardial incompetence. The systolic pressure averaged 118 mm., the diastolic 92 mm., the pulse pressure 26 mm. and the heart load 28 per cent.

In our series of 305 patients showing a maximum systolic pressure of 160 mm. or over, we have estimated the heart load from the average diastolic and pulse pressure readings and divided them into four groups according to the estimated cardiac load. They are as follows: under 40 per cent., seventeen cases; 40 to 60 per cent., eighty-four cases; 61 to 99 per cent., 159 cases; 100 per cent. and over, forty-five cases.

Heart Load Under 40 Per Cent.—The seventeen cases of this group may be divided into two divisions: typical symptoms of chronic nephritis, 11 cases or 64 per cent.; other cases, 6, or 36 per cent.

The eleven cases of chronic nephritis showed the signs of the interstitial variety in seven and the parenchymatous type in four. The systolic pressures were relatively low, exceeding 200 mm. in only two instances, and averaging 180 mm. The diastolic pressures were high, all over 100 mm., and below 120 mm. in only three. The average was 133 mm. Of the seven patients with symptoms of interstitial nephritis,

8. Stone, W. J.: The Archives Int. Med., 1915, xvi, 775.

two showed no signs of cardiac failure, with a heart load of 33 and 38 per cent., respectively. The others showed definite cardiac failure, such as acute dilatation, pulsus alternans and death, dilatation of the heart, auricular flutter and death in uremia, and mitral regurgitation. The four nephritic cases of the parenchymatous type were without any signs of cardiac failure except one case with paroxysmal tachycardia. One patient died of pneumonia and septicemia.

The six cases without chronic nephritis included one with signs of acute nephritis. The heart was negative in two, but in the others there was angina pectoris with cardiac dilatation, displacement of the heart by hydrothorax, mitral regurgitation, and congenital malformation of the heart. The systolic pressures were still lower here, averaging 160 mm., the diastolic pressures averaging 123 mm.

Of these cases with the subnormal cardiac load six died in the hospital or a few weeks after leaving. Two had hemiplegia and one uremia.

Heart Load from 40 to 60 Per Cent.—Stone claims that normally the heart load varies from 40 to 60 per cent. In our hypertension cases there were eighty-four in this group. Seventy-two, or 85 per cent., were cases of chronic nephritis of the interstitial type. In these the heart conditions were as follows: negative, nine cases; hypertrophy without signs of myocardial weakness, forty-three cases; myocarditis without valvular lesions, twelve cases; mitral regurgitation, seven cases; mitral and aortic regurgitation, one case.

There were twelve cases without signs of nephritis. These may be enumerated as follows: meningitis, two; taenia saginata, one; cancer of prostate with metastases, one; general miliary tuberculosis, one; pernicious anemia, one; tabes dorsalis with enlarged heart, one; mucous colitis, one; chronic heart disease, four. Of the heart cases, one was mitral and aortic regurgitation and three were cases of chronic myocarditis.

There were forty-four patients, or more than half, with arteriosclerosis. The diastolic pressure in all the cases averaged from 120 mm. to 140 mm. In only ten cases was it below 100 mm. The average diastolic pressure in the nephritic cases was 122 mm. There were nineteen deaths in this group, uremia occurred in thirteen and cerebral hemorrhages in eight. Of the eighty-four cases, but 28 per cent. gave signs of cardiac decompensation.

Heart Load from 61 to 99 Per Cent.—Under this head are grouped all cases with a moderate overload, less than 100 per cent. Chronic nephritis was present in 118 cases, or 74 per cent., and not present in

forty-one cases, or 26 per cent., making a total of 159 cases. The condition of the heart in the 118 nephritic cases is shown in the following tabulation:

Heart	No.	Heart	No.
Normal	10	Partial or complete block	3
Hypertrophied	40	Angina pectoris	3
Dilated	5	Mitral valve disease	9
Simple chronic myocarditis	15	Aortic valve disease	3
Auricular fibrillation	7	Aortic and mitral valve disease	2
Premature auricular beats	7	Aortic arch dilated	14

Eighty-six of the above cases had more or less arteriosclerosis. There was hemiplegia in seven due apparently to cerebral hemorrhage. Twelve had symptoms of uremia. There were eighteen deaths among nephritic patients as follows: uremia, nine; myocarditis, five; mitral valve disease, one; dilatation of heart, one; cerebral hemorrhage, one; arteriosclerosis, one.

The diagnoses of the 41 nonnephritic cases were as follows:

Diagnosis	No.	Diagnosis	No.
General arteriosclerosis	1	Cardiac hypertrophy[9] with complications	3
Plumbism	1	Dilatation of heart	3
Pulmonary emphysema	2	Gout and myocarditis	1
Cerebellar tumor	1	Heart block	2
Gout and cirrhosis of the liver	1	Mitral regurgitation	3
Hyperthyroidism	3	Mitral and aortic regurgitation	4
Amyotrophic lateral sclerosis	1	Aortic regurgitation	1
Hemiplegia	2	Mitral stenosis	1
Chronic morphin poison	1	Dilatation of aortic arch	1
Cirrhosis of the liver	1		
Chronic myocarditis	8		

The condition of the heart in the forty-one nonnephritic cases was as shown in the following tabulation:

Heart	No.	Heart	No.
Normal	4	Aortic and mitral regurgitation	4
Hypertrophied	11	Mitral regurgitation	3
Myocarditis	8	Aortic regurgitation	1
Dilated	5	Mitral stenosis	1
Heart block	2	Aortic arch dilated	1
Tachycardia (hyperthyroidism)	1		

The deaths that occurred among the forty-one nonnephritic patients were due to the following causes:

Cause of Death	No.
Chronic myocarditis	1
Heart block	1
Acute dilatation of heart	1
Hyperthyroidism and tachycardia	1
Meningitis	1
Total	5

9. The term hypertrophy refers to a heart not showing decompensation, as is the case in myocarditis, but with an increased area of cardiac dulness or ventricular hypertrophy, as indicated by the electrocardiograms.

The condition of the heart in the 159 cases of heart overload of from 61 to 99 per cent. was as follows:

Heart	No.	Heart	No.
Normal	14	Heart block (partial or complete)	5
Hypertrophy	51	Tachycardia (hyperthyroidism)	1
Chronic myocarditis	37	Mitral valve disease	13
Dilatation	10	Aortic valve disease	4
Angina pectoris	3	Aortic and mitral valve disease	6
Aortic arch dilated	15		

Thus, not counting the fourteen normal cases and those with a hypertrophied or enlarged heart, where no definite diagnosis of myocarditis or dilatation was made, we find that ninety-four, or 60 per cent., showed definite signs of heart decompensation.

The deaths among the 159 patients with heart overload of from 61 to 99 per cent. were as follows:

Cause of Death	No.	Cause of Death	No.
Uremia	9	Myocarditis	6
Cerebral hemorrhage	1	Dilatation of heart	2
Arteriosclerosis	1	Heart block	1
Meningitis	1	Mitral valve disease	1
Hyperthyroidism and tachycardia	1		

There were 101 cases of arteriosclerosis, and seventeen out of 145 cases in which a Wassermann test was made were positive.

The diastolic pressure averaged much lower than in the two previous groups. In seventy-seven cases, or almost half, it averaged under 100 mm. In most cases it was between 70 mm. and 110 mm. The average diastolic pressure in the ninety-nine nephritis cases was 110 mm.

Heart Load 100 Per Cent and Over.—These cases had a distinct overload, varying from 100 per cent. to a maximum of 220 per cent. The highest three percentages were 220, 173 and 166, all cases of aortic regurgitation. The remaining had an average load between 100 and 161 per cent. Chronic nephritis was present in thirty-two cases, or 71 per cent., while there was no marked nephritis in thirteen cases, or 29 per cent., a total of forty-five cases.

The condition of the heart in the thirty-two nephritic cases is shown in the following tabulation:

Heart	No.	Heart	No.
Normal	3	Complete heart block	2
Hypertrophied	6	Partial block, aortic arch dilated	1
Hypertrophied and bradycardia	1	Arch dilated, heart hypertrophied	4
Dilated	2	Mitral stenosis	1
Simple chronic myocarditis	6	Mitral and aortic regurgitation	1
Myocarditis, dilatation of aortic arch	1	Aortic regurgitation	4

There was some hemiplegia in five of the above cases, due to cerebral hemorrhage, and there were three with symptoms of uremia.

Of the thirteen nonnephritic cases, there were three in which the heart was negative, one of these being a case of lobar pneumonia, one of splanchnoptosis, and one of cirrhosis of the liver. There were two cases of hypertrophied heart, one accompanied by cerebral arteriosclerosis, the other by obesity. There were two cases of dilatation of the heart and the aortic arch, two of chronic myocarditis, three of aortic regurgitation, and one of aortic and mitral regurgitation and stenosis.

The condition of the heart in these forty-five cases of overload of 100 per cent. and over is shown in the following tabulation:

Heart	No.
Negative	6
Hypertrophied	9
Chronic myocarditis	9
Dilated	4
Heart block, partial or complete	3
Aortic arch dilated	4
Mitral stenosis	1
Mitral and aortic valvular disease	2
Aortic regurgitation	7
Total	45

Thus we find that thirty, or 66 per cent., of the above cases had definite signs of cardiac decompensation. There were seven deaths among these forty-five patients, with overload of over 100 per cent., the cause being as follows: uremia and heart decompensation, three; cancer and hemiplegia, one; dilated arch and hemiplegia, one; aortic regurgitation and hemiplegia, one; and aortic regurgitation, one.

Thus there were three patients who died of uremia and three with hemiplegia. Three of the patients who did not die also had hemiplegia.

There were thirty-two cases, or 71 per cent., of this group with marked arteriosclerosis. In eight out of forty-three cases with an overload over 100 per cent. in which a Wassermann was taken, the test was positive.

The diastolic pressure averaged over 100 mm. in only six cases. In thirty-nine it was less than 100 mm. and in thirty-three cases it was less than 90 mm.

TABLE 3.—HEART LOAD SUMMARY

Heart Load, per Cent.	Number Cases	Per Cent. with Nephritis	Per Cent. with Normal Hearts	Per Cent. with Hypertrophied Hearts	Per Cent. with Decompensated Hearts	Per Cent. Deaths
Under 40	17	64	12	29	59	35
40 to 60	84	85	20	52	28	22
61 to 99	139	74	8	32	60	14
100 and over	45	71	13	19	66	15

ELECTROCARDIOGRAPHIC READINGS

The physical examination of the heart is often obscure in revealing the actual functionating ability of this organ. An electrocardiogram was made in 139 of the patients with hypertension and we have used its readings in making the diagnosis of heart disease. Table 4 is a summary of pressure findings in these cases.

TABLE 4.—Blood Pressure Findings in Various Heart Conditions

Electrocardiogram	Number Cases	Systolic Pressure, Mm.	Diastolic Pressure, Mm.	Pulse Pressure, Mm.	Heart Load, per Cent.
Normal curves	34	171	107	69	71
Left ventricular hypertrophy (uncomplicated)	46	180	111	77	72
Right ventricular hypertrophy (uncomplicated)	4	186	111	72	64
Left ventricular hypertrophy and auricular fibrillation	6	176	98	78	70
Left ventricular hypertrophy, auricular fibrillation and premature ventricular beats	7	175	102	73	71
Left ventricular hypertrophy and premature ventricular beats	11	193	113	80	70
Left ventricular hypertrophy and bradycardia	1	205	90	115	116
Left ventricular hypertrophy, auricular flutter and premature ventricular beats	1	156	103	53	36
Left ventricular hypertrophy and paroxysmal tachycardia	1	152	119	40	33
Right ventricular hypertrophy, auricular fibrillation and premature ventricular beats	3	163	109	54	49
Right ventricular hypertrophy and auricular fibrillation	1	135	79	51	64
Complete block	3	190	95	103	110
Complete block and left ventricular hypertrophy	2	184	110	75	75
Delayed conduction or partial block with left ventricular hypertrophy, auricular flutter and ectopic ventricular beats	5	205	110	83	71
Auricular fibrillation, auricular flutter or premature ventricular beats	14	167	87	80	91
Total cases	139	...	...	...	...

There is no very obvious effect on the blood pressure from the various abnormalities revealed by the electrocardiogram. The cases all showed more or less evidence of cardiac decompensation, so that the heart load was generally greater than normal. The pulse pressure,

diastolic pressure and systolic pressure were all moderately high. In the cases of right ventricular hypertrophy the heart load is almost normal, averaging lower than all the other types of abnormality. The cases of complete block are notable for the high pulse pressure associated with increased cardiac load. When complete block was associated with left ventricular hypertrophy this condition was present in only one of the two cases. In partial block the heart load was considerably less. Where there was auricular fibrillation, auricular flutter or premature ventricular beats without ventricular hypertrophy, there was a lowering of both systolic and diastolic readings, while the pulse pressure and the heart load were high; evidence of severe decompensation.

MAXIMUM DIASTOLIC PRESSURE

Many authors agree as to the importance of diastolic readings, but there is little literature in which cases have been studied especially from this point of view. Stone[6] states that diastolic pressure is a better index of hypertension than the systolic. A sustained pressure of from 100 to 110 signifies hypertension, and it is less influenced by physiologic factors. Warfield[10] believes that the diastolic reading is the most important. A high diastolic reading means constant increased work for the heart and leads to hypertrophy of the left ventricle. A high systolic pressure is invariably associated with a high diastolic pressure, and in failing heart the systolic pressure approaches the diastolic till the pulse pressure becomes nil. He states that it is now generally conceded that high diastolic, high systolic and increased pulse pressure indicate chronic interstitial changes in the kidneys, in the face of normal urinary findings.

In view of the above reference to hypertrophy of the left ventricle, it is interesting to refer to our electrocardiographic findings. Out of the 139 cases the general average of diastolic readings was considerably above normal, even in those without evidence of a predominant left ventricle. There were, however, 57 per cent. in which the electrocardiogram showed left ventricular hypertrophy.

Stone also emphasizes the importance of the diastolic pressure, which represents the constant pressure between systoles. He believes that it is a better index of peripheral resistance and of hypertension than the systolic pressure. A sustained diastolic pressure of from 105 mm. to 110 mm. or above signifies hypertension, irrespective of the height of the systolic pressure, and the diastolic is less influenced by physiologic factors than the systolic pressure. Janeway,[11] on the other hand, has declared that except in cases of aortic regurgitation, marked

10. Warfield: New York Med. Jour., 1915, cii, 509.
11. Janeway: Am. Jour. Med. Sc., 1906, cxxxi, 772.

bradycardia and the senile pulse, when the diastolic pressure must be determined before hypertension can be diagnosed, the diastolic pressure is not of very great value. In 305 cases with systolic pressure of 160 mm. or over the diastolic pressure was as shown in the following tabulation:

Maximum Diastolic Pressure, Mm.	No. Cases	Maximum Diastolic Pressure, Mm.	No. Cases
51 to 60	1	131 to 140	37
61 to 70	5	141 to 150	30
71 to 80	5	151 to 160	17
81 to 90	22	161 to 170	11
91 to 100	34	171 to 180	3
101 to 110	50	181 to 190	2
111 to 120	50	191 to 200	2
121 to 130	35	205	1

Thus, in 305 cases with a maximum systolic pressure of 160 mm. or over, 32 per cent. showed a diastolic pressure of from 101 mm. to 120 mm., while the readings gradually shaded off to 60 mm. as the minimum and 205 mm. as the maximum. Many cases, however, did fall to a lower diastolic pressure than 60 mm. during their stay in the hospital.

Maximum Diastolic Pressure of 60 mm.—The diastolic in this one case fell as low as 40 mm. There was a high pulse pressure, caused by syphilitic aortitis, with aortic regurgitation and a slight glomerular nephritis, as proved by necropsy.

Maximum Diastolic Pressure from 61 to 70 mm.—This subnormal reading occurred in five cases, in four of which there was marked aortic regurgitation, while in the fifth there was marked arteriosclerosis and dilatation of the aortic arch. Nephritis was not present at all, or there was merely a mild secondary involvement of the kidneys.

Maximum Diastolic Pressure from 71 to 80 mm.—The five cases in this class were aortic regurgitation with a mild secondary nephritis, a case of myocarditis with chronic bronchitis, cirrhosis of the liver, diabetes mellitus and one mild case of chronic nephritis, in which the phenolsulphonephthalein rose from a minimum of 32 per cent. to 57 per cent.

Maximum Diastolic Pressure from 81 to 90 mm.—Though these readings are above the normal of 80 mm., yet for a systolic pressure of 160 mm. or over they are relatively low. Sixteen of these cases gave no signs of any marked nephritis. The phenolsulphonephthalein test was made in a few and ranged from 50 to 70 per cent. The majority showed an enlargement of the heart, and there were two cases of aortic regurgitation. There were six cases of nephritis. The low diastolic reading may be explained in all of these, however. Two patients were

in a late stage of the disease and died a few days after admission. In one the primary condition was diabetes mellitus and the nephritis was but a mild one as indicated by a phenolsulphonephthalein reading of 63 per cent. The fourth case was one of hyperthyroidism, with marked cardiac decompensation and auricular fibrillation. In the fifth case the low diastolic pressure was accounted for by the evidence of a dilated aortic arch. Finally, there was one case with chronic interstitial nephritis, with a phenolsulphonephthalein output of 28 per cent. and 34 mg. of blood urea nitrogen in 100 c.c. of blood, but in this case there was complete heart block and a bradycardia of 30 to 40 beats.

Maximum Diastolic Pressure from 91 to 100 mm.—Of the thirty-four cases in this group showing a moderate diastolic hypertension, there were fourteen without nephritis and twenty with it. In the non-nephritic cases the phenolsulphonephthalein test, taken in most of them, gave readings of from 52 to 89 per cent. In two there was aortic regurgitation with some involvement of the mitral valve; in others there were other cardiac lesions, a case of emphysema and tumor of the brain. In a few the hypertension was not explained.

In an advanced form of chronic interstitial nephritis one would expect a high diastolic reading. There were five of these, as indicated by a phenolsulphonephthalein reading of from 0 to 20 per cent. Four of these patients died in the hospital and one had auricular fibrillation. Cardiac decompensation was present in all of these. In seven the phenolsulphonephthalein was moderately low, from 20 to 40 per cent. The low diastolic reading was explained in two of these by the presence of aortic regurgitation, in three by a chronic myocarditis with auricular fibrillation. In one there was a cerebral hemorrhage, and in one there was nephritis without signs of decompensation. The remaining cases of nephritis were mild with phenolsulphonephthalein of over 40 per cent.

Thus, in those with only a moderately high diastolic pressure nephritis is frequently observed, but one may expect to find only a mild grade, as indicated by the phenolsulphonephthalein test, or else very advanced disease with broken cardiac decompensation.

Maximum Diastolic Pressure from 101 to 120 mm.—Of the 100 cases in this group, fifty-six were diagnosed as chronic nephritis. In the 44 per cent., however, in which a diagnosis of nephritis was not made, the hypertension was no doubt due to changes in the kidneys, this condition being overlooked by the dominance of other pathologic processes. Thus, in half of these nonnephritic cases a phenolsulphonephthalein test was made, and in ten the reading was between 22 and 50 per cent. In the remainder the hypertension may be explained wholly or in part by such conditions as advanced arteriosclerosis, myo-

carditis, alcoholism, chronic lead poisoning, mitral valvular disease, angina pectoris, hyperthyroidism, cerebral hemorrhage, and cirrhosis of the liver.

Most of the fifty-six renal cases in this group showed a fairly advanced stage of renal interstitial processes, as indicated by the phenolsulphonephthalein output. This was as follows:

No. Cases	Phenolsulphonephthalein, %
3	No record
4	0
7	1 to 19
24	20 to 40
18	40 to 61

There were five cases of lead poisoning in this group, but only three, or 3 per cent. of the group, showed aortic regurgitation.

Maximum Diastolic Reading from 121 to 150 mm.—Of the 102 patients included in this group, only ten, or about 9 per cent., were not diagnosed as having chronic nephritis, but in four of these the phenolsulphonephthalein read from 10 to 50 per cent., so that there was some impairment of kidney function. The remaining six cases were generalized arteriosclerosis, aneurysm with aortic regurgitation, chronic myocarditis, syphilis with enlarged liver and spleen, renal calculus with mitral regurgitation, and arteriosclerosis with dilated aortic arch.

About 91 per cent. of the patients gave very definite signs of chronic nephritis, with albuminuria, hypertrophy of the heart and uremia. In eighty-seven of these cases the phenolsulphonephthalein read as follows:

No. Cases	Phenolsulphonephthalein, %
17	0
7	1 to 10
18	11 to 30
17	31 to 40
13	41 to 50
15	51 to 62

Among the nephritic cases there were two cases of aortic regurgitation, making three altogether, with a diastolic pressure between 121 and 150 mm.

Maximum Diastolic Pressure from 151 to 170 mm.—Among the twenty-eight cases in this group there was but one without definite signs of nephritis. The diagnosis in the case of this patient was tabes dorsalis. There was no albuminuria, the heart was normal, but arteriosclerosis was present. The hypertension in this patient may be explained in part at least by severe gastric crises.

The remaining twenty-seven patients had definite signs of chronic nephritis, with hypertrophy of the heart. There was one with a phenolsulphonephthalein output of 60 per cent., and this patient had syphilitic

aortitis. There were two cases of hemiplegia, an additional one with a cerebral hemorrhage. The phenolsulphonephthalein test was performed in twenty-five of the cases. In the two in which this test was not performed the blood urea nitrogen was 79 mg. and 181 mg., respectively. There was no case of aortic regurgitation. The results of the test in these twenty-five cases are as follows:

No. Cases	Phenolsulphonephthalein, %
4	0
2	1 to 10
4	11 to 20
10	21 to 40
4	41 to 50
1	60

Maximum Diastolic Pressure from 171 to 200 mm.—Seven cases fell in this group, all of which were cases of chronic nephritis, as confirmed by necropsy in three. A phenolsulphonephthalein test was made in all. There was no excretion from one; 1 to 10 per cent. in three; from 11 to 20 per cent. in two, and 23 per cent. in one. There was fatty degeneration of the heart in two of the necropsied cases and the retromanubrial dulness was increased in two. Arteriosclerosis was present in all.

Maximum Diastolic Pressure 205 mm.—There was but one case with so high a maximal diastolic pressure. The systolic pressure in this case was 240 mm. There was chronic nephritis with a phenolsulphonephthalein of 48 per cent., complicated by a hemiplegia involving the left leg and arm.

TABLE 5.—Comparison of Maximum Diastolic with Systolic Pressure

Maximum Diastolic Pressure, Mm.	Average of Maximum Systolic Pressure, Mm.	Number Cases	Per Cent. Cases Nephritis	Aortic Regurgitation, Number Cases
60	150	1	0	1
61 to 70	(160-170)	5	0	4
71 to 80	173 (160-185)	5	20	1
81 to 90	180 (160-250)	22	27	2
91 to 100	184 (160-250)	34	58	4
101 to 120	190 (160-260)	100	56	3
121 to 150	215 (168-290)	102	91	3
151 to 170	205 (180-280)	28	96	0
171 to 200	262 (230-300)	7	100	0
205	240	1	100	0

Table 5 indicates the progressive increase in the percentage of chronic nephritis in proportion to the rise in diastolic pressure. By averaging the corresponding maximum systolic pressures we note a less regular rise in the systolic pressures. The pressure of 160 mm. appears several times in the groups in which 20, 27, 58 and 56 per cent. of the cases are chronic nephritis. While of course a high systolic pressure suggests the presence of chronic nephritis, a diastolic pressure of 120 mm. and over is very strong evidence of the presence of this condition, and one may expect more than half the cases to show evidence of chronic Bright's disease if the diastolic pressure reaches from 90 to 120 mm. A subnormal diastolic pressure, or one below 80 mm., is rarely associated with a chronic nephritis.

VARIATIONS IN PRESSURE DURING TREATMENT

Norris[12] states that rest causes a decrease in systolic, diastolic and pulse pressure. All of the patients in our series were put to bed for a few days at least. In general, the first systolic pressure taken was very high. Patients who remained in the hospital had numerous records taken and these were charted. In some cases the reading was made daily or every two days. It thus was very easy in most cases to tell at a glance the tendency of systolic, diastolic and pulse pressure to increase or decrease. Most cases showed a definite tendency up or down, but in some there was a distinct rise after a progressive fall, to be followed again by a fall. These cases we have classed with certain cases in which there was little if any variation. Hecht[13] has shown the marked effect of sanatorium and hospital treatment in reducing the pressure, which again becomes elevated on resuming natural life conditions. This was repeatedly verified in patients who returned for a second, third or fourth visit to the hospital. In our statistics several factors came into play in causing variations in the pressure. Above all, rest with a restricted diet tended to lower hypertension. A few cases were definitely influenced by digitalis, but as a rule this influence was only temporary and therefore not considered in our table. Nitrites were seldom given and their effect was fleeting. Most of the patients who died showed a progressive fall in systolic and diastolic pressure during the last weeks of life. The following tabulation shows the variations in 304 cases:

	No. Cases with Tendency to Rise	No. Cases with Tendency to Fall	No. Cases Fluctuating or Maintained
Systolic pressure	40	190	74
Diastolic pressure	43	181	80
Pulse pressure	71	151	82

12. Norris: Blood Pressure, Its Clinical Applications, Philadelphia, Lea & Febiger, 1914.

13. Hecht: Ztschr. f. klin. Med., 1912, lxxvi, 87.

We see from the above table that there is a marked tendency for the systolic pressure to fall or remain high; the diastolic pressure is also most likely to fall, but it is more likely than the systolic to remain stationary or rise, while pulse pressure generally falls, but is more likely to rise or remain unchanged than the other two. The greatest fluctuations were usually to be found in systolic readings, and the least in pulse pressure. In some cases, however, the greatest changes were observed between the maximum and minimum pulse pressure or diastolic pressure.

DIGITALIS AS AFFECTING PRESSURE

In hypertension cases digitalis is of distinct value when decompensation of the myocardium has set in. Theoretically, as Norris[12] says, digitalis should increase tension, especially in hypotension cases. Clinically, however, it is often found to lower the pressure, and is of especial value in failing heart, in which case it may lower tension by increasing the elimination of urine or by decreasing venous stasis.

In our cases digitalis was used to restore broken heart compensation. If only a few doses were given the effect was naturally only transient. There were sixty-nine patients, however, in whom digitalis seemed to have a definite influence on the pressure curves, as proved by a careful comparison of the dates when digitalis was started and stopped with the blood pressure chart. In these sixty-nine cases the heart and circulatory system showed the following conditions:

Conditions Found	No. Cases
Myocarditis and decompensation	22
Chronic nephritis and cardiac decompensation	31
Chronic nephritis without cardiac disease	9
Angina pectoris	5
Arteriosclerosis	1
Hyperthyroidism	1

	No. of Cases Tendency to Rise	No. of Cases No Change	No. of Cases Tendency to Fall
Systolic pressure	43	6	20
Diastolic pressure	23	12	32
Pulse pressure	44	15	10

In fourteen cases there was a progressive rise in systolic, diastolic and pulse pressure. In five they all fell synchronously.

It was a common occurrence to note, following the administration of digitalis, a marked increase in the systolic and pulse pressure, the latter often being largely caused by the fall in diastolic pressure. The rise in systolic pressure caused an improvement in symptoms and the general condition of the patient.

DEATHS

According to Norris[12] a systolic pressure of 180 mm. is not often exceeded without symptoms, and constant pressures of 200 mm. or over are generally not long maintained before leading to some catastrophy, such as angina pectoris, uremia or apoplexy.

Janeway[2] analyses the deaths of 212 of his private patients who at some time prior to death had a systolic pressure above 160 mm. Of these, 32.6 per cent. died "a gradual cardiac death," while in his cerebral group there were 40.8 per cent. The majority of deaths occurred between the age 40 and 60 years. He also says that a systolic pressure above 200 mm., other things being equal, constitutes a certain presumption in favor of death by uremia or apoplexy. Finally, he concludes as follows:

> Death in this type of cardiovascular disease, among patients in private practice, occurs in the followings ways, arranged in the order of their frequency: First, by gradual cardiac insufficiency; second, with uremic symptoms; third, by apoplexy; fourth, from some complicating acute infection; fifth, in an attack of angina pectoris; sixth, from purely accidental and unrelated causes; seventh, in a paroxysm of acute edema of the lungs; eight, after the manner of cachexia.

In our series, fifty-two deaths occurred while the patients were under treatment in the hospital, or a few days after their discharge. Other patients died at their homes or in other institutions, but the exact facts attending their final illness being uncertain, they are not included in our list.

Of the fifty-two cases, a postmortem was performed in thirty-one. In twenty-one this was not possible, but every other means available was made use of to determine the nature of the disease. Eight patients were under observation for less than one week. The remainder were watched for periods varying from eight days to two years. The age of these fifty-two patients at the time of death is shown in the following tabulation.

Age, Years	No. Cases	Per Cent.
70 to 76	3	5.7
61 to 69	9	17.3
40 to 60	26	50.0
30 to 39	7	13.3
20 to 29	4	8.0
16 to 19	3	5.7

The greatest number of deaths occurred between the ages 40 and 60 years, and the next most commonly between the ages 61 and 69 years. The next period in point of frequency was the period from 30 to 39 years. The youngest person who died was 16 and the oldest 76 years.

The dominant pathologic conditions as diagnosed before death or proved by necropsy are shown in the following tabulation:

Conditions Found	No. Cases
Chronic nephritis	16
Chronic nephritis and myocarditis	16
Chronic nephritis and pulmonary tuberculosis	1
Chronic nephritis and intestinal obstruction	1
Chronic nephritis and lobar pneumonia	1
Chronic nephritis and aortic insufficiency	2
Chronic myocarditis	5
Chronic myocarditis and angina pectoris	1
Heart block	1
Endocarditis of mitral, tricuspid and aortic valve	1
Carcinoma of lung	1
General carcinomatosis, metastases	3
Syphilitic (?) meningitis	1
Hemorrhagic meningo-encephalitis	1
General miliary tuberculosis	1

There were therefore thirty-seven cases in which there was marked chronic nephritis, usually of the interstitial variety, and ten cases in which there was serious derangement of the circulatory system. In seven, any cardiorenal lesions that existed were of such a secondary nature as to cause no comment in the record of the patient. The apparent cause of death in these fifty-two cases is shown in the following tabulation:

Apparent Cause	No. Cases	Apparent Cause	No. Cases
Uremia	24	Anginal attack	1
Heart failure	11	Venous thrombosis	1
Terminal apoplexy	5	Miliary tuberculosis	1
Acute cardiac dilatation	3	Pregnancy	1
Obstruction to bronchus (cancer)	2	Pneumonia and septicemia	1
Meningitis	2		

The above patients were very carefully observed during the last days of life, so that the data, often confirmed by necropsy, are as accurate as it is possible to make them. Twenty-nine patients, or about 55 per cent., died with cerebral symptoms, uremia or apoplexy. Fifteen, or about 28 per cent., died with progressively or suddenly impaired heart function, following some preexisting cardiac lesion. Two died of respiratory failure due to mechanical obstruction. The two cases of meningitis might be included with the cerebral group. In one, pregnancy proved to be the last straw in a patient with chronic myocarditis and nephritis.

Systolic Pressure in Fatal Cases.—Twenty-eight, or about 53 per cent. of the patients who died, gave a maximum systolic pressure of 200 mm. or over. Most of these died with uremic symptoms, only three of those dying having given a systolic reading less than 200 mm. The other patients with a maximum pressure of less than 200 suffered from cardiac disease, tuberculosis, meningitis, cancer, etc.

Diastolic Pressure in Fatal Cases.—Forty-five, or about 86 per cent., had a diastolic pressure of 100 mm. or above. These included most of the patients with chronic nephritis who died of uremia. There were seven whose diastolic pressure never reached 100 mm. One died of carcinoma; two of endocarditis of the aortic valve; two of myocarditis with thromboses; one of uremia from chronic interstitial nephritis; and one of meningitis. The variations in blood pressure in the fifty-one patients who died is shown as follows:

	Systolic Pressure	Diastolic Pressure	Pulse Pressure
Rose	11	9	15
Maintained about same	16	17	15
Fell	24	25	21

The variations in these patients are not strikingly different from the variations that generally occur in patients with hypertension who do not die. Of course the readings just ante mortem are not counted here, but the tendency of the pressure to rise or fall during the patients' stay in the hospital. The tendency of the systolic, diastolic and pulse pressure was certainly less towards a fall than it was in the whole group of cases taken together.

CONCLUSIONS

1. In the wards of a general hospital hypertension occurs almost as frequently in females as in males.

2. About 68 per cent. of cases of hypertension are found in patients between 40 and 69 years of age, the greatest number occurring between the ages 50 and 59 years.

3. Almost three fourths of the cases, 72.8 per cent., had definite signs of chronic nephritis. Arteriosclerosis was also common. The next most common conditions were circulatory disturbances, chronic myocarditis or valvular lesions.

4. If several specimens of urine are examined, albumin is usually to be found at some time in cases of hypertension. If it is persistently absent, the cause of the high blood pressure is generally vascular or cardiac disease, and not renal.

5. The readings of the phenolsulphonephthalein test vary inversely with the average systolic and diastolic readings, this ratio being especially noticeable in the case of diastolic readings.

6. The blood urea nitrogen varies directly with the average systolic and diastolic readings.

7. In hypertension cases with a normal heart load of 40 to 60 per cent., 85 per cent. had chronic nephritis. Of those cases in which the load was under 40 or over 60 per cent., only about 70 per cent. were cases of nephritis. When the load was under 40 per cent., the

prognosis proved to be most unfavorable, but there were several cases without signs of cardiac decompensation. Among those whose heart load was 40 to 60 per cent., only 28 per cent. gave signs of cardiac decompensation; of those whose heart load was 61 to 99 per cent., there were 59 per cent. with cardiac decompensation, and of those whose load was 100 per cent. or more, 66 per cent. showed signs of cardiac decompensation. Hypertrophy of the heart without decompensation was most common in cases with a normal load; when the load was 100 per cent. or over, there were the fewest cases of heart hypertrophy without decompensation and the greater number of decompensated hearts.

8. Subnormal diastolic pressures suggest the presence of aortic regurgitation and the absence of chronic nephritis. With the rise in diastolic pressure the incidence of aortic regurgitation rapidly decreased and the percentage of nephritis steadily increased, much more consistently than when the systolic pressure alone was examined.

9. During the hospital treatment there was usually a decrease in the systolic, diastolic and pulse pressures, but this was more frequent with the systolic than the diastolic or pulse pressure. The pressures may rise or remain about the same.

10. In cardiac decompensation the effect of digitalis was rather to increase pulse pressure and systolic pressure and cause a fall in the diastolic pressure.

11. Deaths in hypertension patients most frequently occurred between the ages of 40 and 60 years, and the underlying condition was either chronic nephritis or chronic disease of the heart, or a combination of the two. More than half the deaths occurred with symptoms of uremia or apoplexy. Twenty-eight per cent. died with signs of progressive heart failure. The patients in more than half the fatal cases had had a systolic pressure of over 200 mm., and 86 per cent. had had diastolic pressure of over 100 mm.

I desire to express my appreciation to Dr. Henry A. Christian, Physician-in-Chief of the Peter Bent Brigham Hospital, under whose direction this work was undertaken, and to Dr. Francis W. Peabody for their valuable suggestions.

THE SUBSEQUENT HISTORY OF PELLAGRINS IN SPARTANBURG COUNTY, S. C., WHO SURVIVED THE INITIAL ATTACK*

J. F. SILER, M.D., P. E. GARRISON, M.D.,
AND
W. J. MACNEAL, M.D.
NEW YORK

INTRODUCTION

In a preceding paper of this series[1] we have discussed the initial attacks of pellagra in 1,180 cases in Spartanburg County in relation to race, sex and age. The death rate in the year of initial attack for these cases was 15.8 per cent. In the present paper we purpose to consider those patients in this same series who survived the year of initial attack, more particularly in regard to their freedom from recurrences in subsequent years, the appearance of such recurrences, the death rate in recurrent attacks and the relation of these phenomena to the duration of the disease. In a subsequent paper we purpose to discuss their relation to race, sex, age, complicating disorders, diet and medicinal treatment. It is hoped that definite criteria may thus be afforded for prognosis in pellagra, for this particular geographical district at any rate. So far as we are aware there are in the literature no reported observations on a large series of noninstitutional pellagrins followed over a period of years, although there are reports of successful treatment of rather large series of cases in a single year and of institutional pellagra during a series of years.

RECURRENT ATTACKS APPEARING IN EACH YEAR

The total number of recurrent attacks of pellagra (with erythema) recorded as occurring in each year in the pellagrins of this series is shown in Table 1, together with the total incident attacks recorded in each year, for comparison. The recorded recurrences have increased

* Submitted for publication May 12, 1916.

* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* This paper has been written since Dr. Garrison and Dr. Siler were recalled to active duty in the Medical Corps, U. S. Navy, and the Medical Corps, U. S. Army, respectively. Although they are quite familiar with the general nature of the paper, they are not personally responsible for the detailed compilation of data or for the specific deductions drawn from them.

1. Siler, Garrison and MacNeal: The Incidence of Pellagra in Spartanburg County, S. C., and the Relation of the Initial Attack to Race, Sex and Age. THE ARCHIVES INT. MED., 1916 (in press).

progressively every year, and although the data in regard to recurrences in 1914 are undoubtedly less complete than for 1912 and 1913, nevertheless the highest number of recorded recurrences, namely, 250, was in 1914. This adds confirmation to our conclusion, based on the study of the incident cases, that pellagra has been steadily and progressively increasing in Spartanburg County since 1908. It is interesting to note that the number of pellagrins with recurrence of the disease is nearly equal to the number with initial attacks, not in the same year, but in the preceding year, in each instance. In fact, the agreement is remarkably close in the years since 1909. In that year there were fifty-seven recorded initial attacks and in 1910 there were fifty-eight pellagrins with recurrences. In 1910 there were 141 initial attacks and in 1911 there were 141 recurrences. In 1911 there were 234 initial attacks, followed by 230 recurrences in 1912. In 1912 there were 211 initial attacks and in 1913 there were 238 pellagrins who had recurrences. In 1913 the initial attacks numbered 251 and in 1914 the pellagrins with recorded recurrences numbered 250. This agreement would seem to be more than accidental, and it suggests that the individuals newly attacked in one year make up a very important part of the persons showing recurrences in the following year. We shall subsequently have opportunity to inquire into this relationship in more detail.

TABLE 1.—Distribution of Pellagrins Who Had Recurrent Attacks of Pellagra in Spartanburg County According to Year of Recurrence and of Incident Pellagrins According to Year of Onset

Year	Before 1908	1908	1909	1910	1911	1912	1913	1914	Totals
Recurrent pellagrins.....	80	22	34	58	141	230	238	250	1,053
Incident pellagrins.....	57	20	57	141	234	211	251	209	1,180

For the purpose of a comparative study the record of each pellagrin after the year of initial attack has been tabulated for each year under one of the four following headings:

1. Recurrent attack, which indicates the presence of the diagnostic erythema during the respective year.

2. Living without recurrence, which indicates that the patient was free from definite symptoms of pellagra during the respective year.

3. Dying without recurrence, which indicates that the patient died after January 31 of the respective year without definite signs of a recurrent attack.

4. Uncertain, which indicates that the patient passed from observation or gave vague and indefinite evidence of a recurrent attack.

To complete the tabulation it was necessary also to include the instances of death during recurrent attack, as these patients would, of course, be without record in subsequent years. In every instance a death occurring in January has been credited to the preceding year.

The record of the fifty-seven pellagrins incident previous to 1908 is difficult to present in tabular form, and part of these cases will therefore be considered briefly according to the year of onset.

In 1888 Pellagrin 1263, a white man, aged 44, suffered his first attack. He had a recurrence in 1889 and died in that year.

In 1892 Pellagrin 20, a white man, aged 62, had his first attack of pellagra. When seen by us in 1912 he stated that he had had a recurrent attack every year since 1892. He had a definite attack of pellagra in 1912 and died Feb. 27, 1913, without a recurrence of the erythema in that year.

In 1893 Pellagrin 533, a white woman, aged 41, suffered her first attack of pellagra. She had recurrence in 1894 and again in 1895, with recovery. Subsequently she remained well until 1913, when she again suffered a very typical attack of pellagra and was seen by us. She was a very intelligent woman of the moderately well-to-do class, and was quite certain that the manifestations present in 1913 were identical with those she had observed twenty years before. The physician who attended her in the previous attack was also consulted by us. He did not remember any signs of pellagra, but thinks that he may well have overlooked them at that time, as his attention was directed especially to other pathologic conditions in the patient. This woman recovered from the attack in 1913 and remained free from recurrence in 1914 and 1915.

In 1894 Pellagrin 1086, a white girl, aged 15, had her first attack of pellagra. She died in 1889, the assigned cause of death being cancer of the tongue. The history of recurrent attacks of pellagra is indefinite and uncertain. Pellagrin 805, a white woman, aged 31, died of pellagra during her first attack in 1894.

In 1898 Pellagrin 1223, a white man, aged 54, suffered his initial attack of pellagra. The disease recurred each year to 1908, in which year he committed suicide by drowning.

In 1900 Pellagrin 1187, a white man, aged 33, developed pellagra. He had recurrences each year to and including 1906. In 1907 and 1908 the evidence of recurrence is uncertain. The disease recurred definitely in 1909 and each year until death during a recurrent attack in 1911. In 1900 also, Pellagrin 633, a white man, aged 48, suffered his first attack, with recurrence in 1901 and 1902. From 1903 to 1909, inclusive, a period of seven years, there was no recurrence. The eruption reappeared each year in 1910, 1911 and 1912. In 1913 and 1914 there was no recurrence. This patient was an inmate of the Columbia

State Hospital for the Insane in 1912 and part of 1913. In 1914, when seen by us, he seemed quite clear in his mind. Pellagrin 352, a white woman, aged 23, developed pellagra in 1900 and had recurrent attacks in 1901, 1902 and 1903, with death at the Columbia State Hospital for the Insane in 1903.

In 1901 there were also three recorded initial attacks. Pellagrin 354, a white girl, aged 16, developed pellagra in that year and suffered recurrent attacks each year to the end of 1909. She died Feb. 7, 1910, without erythema. Pellagrin 1272, a white man, aged 40, died of pellagra in May, 1901, apparently during the initial attack. Pellagrin 876, a colored woman, aged 53, also died in an initial attack of pellagra in 1901.

In 1902 two new cases were recognized. Pellagrin 426, a white woman, aged 24, died in an initial attack in this year. Pellagrin 1223, a white man, aged 56, developed the disease in 1902 and had recurrences each year to 1906, inclusive, dying in 1906.

All these fourteen patients with onset previous to 1903 furnished, therefore, forty-eight instances of recurrence, seventeen instances of a year without recurrence and five instances of uncertain record up to 1907, inclusive. Of the fourteen patients, eight died before 1908, four in the year of onset, three during the year of recurrence and one during the year without recurrence.

In 1903 there were recorded six incident cases; in 1904 there were five. There were ten in 1905, six in 1906 and fourteen in 1907. In two cases incident before 1908 it was not possible to ascertain the year of origin. These were both colored women, Pellagrins 1260 and 1261, and were said to have died in the initial attack of pellagra at the ages of 16 and 36 years, respectively, some time previous to 1908. The subsequent fate up to 1914 of the forty-one cases incident from 1903 to 1907, inclusive, is shown in detail in Figures 2, 3 and 4, and their behavior up to 1908 is summarized in Table 2. This group of 41 cases furnished fifty-three instances of recurrence, three instances of non-recurrence and twenty-four instances of uncertain record during the years 1904 to 1908, inclusive. Of the forty-one patients, seven died in the initial attack, four died in the year of recurrence and one died in a year in which there was no recurrence. There remained twenty-nine of the forty-one patients alive at the end of 1908. Up to the end of 1907 these forty-one patients furnished seven instances of death in initial attack, thirty-two instances of recurrence, three deaths in recurrence, two instances of survival of a year without recurrence, one instance of death during a year without recurrence and sixteen instances of year without definite record. Adding to these figures the analogous data for the fourteen patients with onset previous to 1903 and the two patients with onset in unknown years, we get a result which

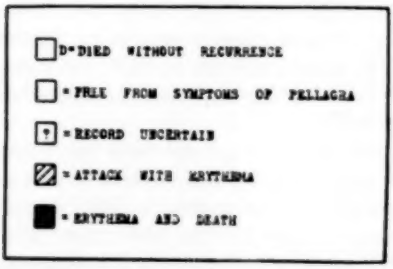
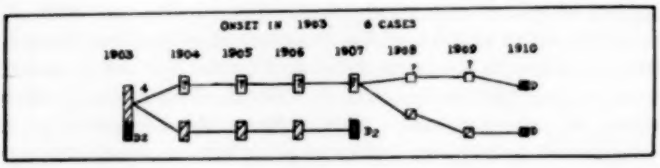


Fig. 1.—This key indicates the manner in which the behavior of each pellagrin is designated in the subsequent figures.

TABLE 2.—Subsequent History up to 1908 of the Forty-One Pellagrins with Onset from 1903 to 1907, Inclusive

	1903	1904	1905	1906	1907	1908	Totals
Initial attacks	6	5	10	6	14	..	41
Death in year of onset	2	0	0	2	3	..	7
Pellagrins with recurrence	..	2	6	11	13	21	53
Death in year of recurrence	..	0	1	1	1	1	4
Pellagrins living without recurrence	..	0	0	1	1	1	3
Pellagrins dying without recurrence	..	0	0	1	0	0	1
Pellagrins without definite record	..	2	3	5	6	8	24
Pellagrins alive at end of year	4	9	18	20	30	29	..
Pellagrins considered in year	6	9	19	24	34	30	..



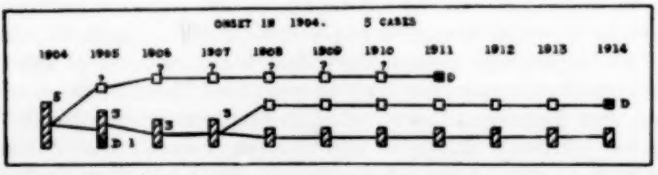


Fig. 2.—Behavior during subsequent years of pellagrins with onset in 1903 and 1904. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

shows fifty-seven pellagrins with onset before 1908, furnishing thirteen instances of death in year of onset, eighty instances of recurrence, seven deaths in a year of recurrence, nineteen instances of survival of a year without recurrence, two deaths in a year in which there was no recurrence and twenty-one instances of a year without definite record. At the end of 1907 there remained alive thirty-five of the fifty-seven patients with onset previous to 1908, and of these there were six who contracted pellagra previous to 1903, eighteen with onset from 1903 to 1906, inclusive, and eleven with onset in 1907.

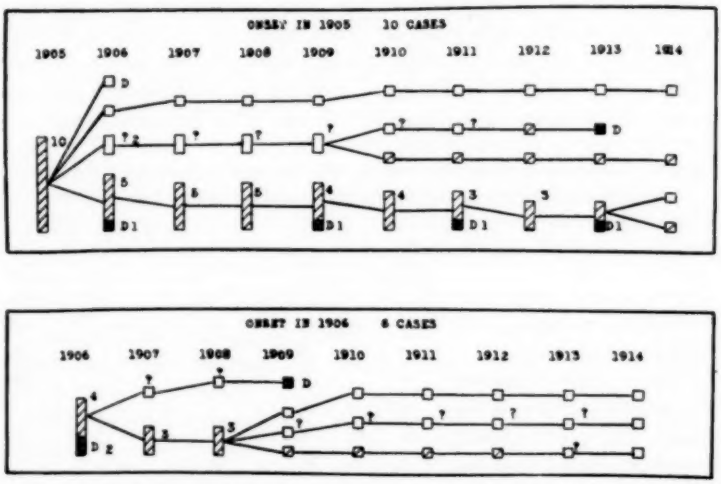


Fig. 3.—Behavior during subsequent years of pellagrins with onset in 1905 and 1906. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

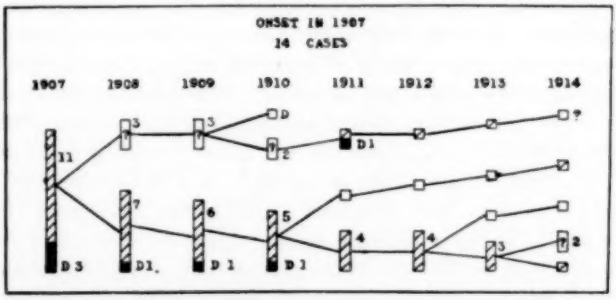


Fig. 4.—Behavior during subsequent years of pellagrins with onset in 1907. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

The fate of these thirty-five survivors during the period 1907 to 1914 is summarized in Table 3.

The table shows a distinct tendency for the number of recurrences to diminish in the later years, while the relative proportion of those who escape without recurrence tends to increase. Thus, in 1908 there were twenty-two with recurrence and four who escaped, a ratio of 5½ to 1. In 1912 this ratio became 3 to 1; in 1913 it was 2 to 1 and in 1914 it became 1 to 1. The ratio of recurrences to escapes from recurrence for all years was 193 to 55, or approximately 3½ to 1 for this group of cases. It is probable that those pellagrins who acquired the disease in these early years and then recovered would be less likely to appear in our records than would those who showed numerous recurrences, and therefore we are inclined to consider this ratio as somewhat too large rather than too small. The indicated death rate

TABLE 3.—Subsequent History up to 1914 of the Thirty-Five Pellagrins with Onset Previous to 1908 Who Remained Alive Feb. 1, 1908

	Before 1908, Total	1908	1909	1910	1911	1912	1913	1914	Totals
Pellagrins with recurrence.....	80	22	20	19	18	15	12	7	193
Deaths in year of recurrence.....	7	2	3	3	4	0	2	1	22
Pellagrins living without recurrence	19	4	5	4	5	5	6	7	55
Pellagrins dying without recurrence	2	0	0	2	0	0	1	0	5
Pellagrins without definite record...	21	9	8	5	2	1	2	4	52
Pellagrins alive at end of the year..	35	33	30	25	21	21	18	17	....
Pellagrins considered in the year....	44	35	33	30	25	21	21	18	....

in recurrence for this whole group of cases was twenty-two in 193, or 11.4 per cent. This figure is probably too low rather than too high, because some of these early fatal cases were doubtless recorded as deaths in initial attack, when, as a matter of fact, there had been an unrecognized attack in a previous year. The indicated death rate in initial attack for the fifty-seven pellagrins incident before 1908 was 22.8 per cent. and, as was pointed out in the preceding paper of this series, we regarded this figure as too high for this same reason. This criticism does not apply, however, to the events subsequent to 1907 in this group, and even here the deaths have been fifteen in a total of 113 recurrences, or 13.1 per cent. Certainly, this would indicate that pellagra is not a disease of progressive degeneration presenting a more unfavorable prognosis the longer it has existed in the patient, but rather that the danger to life in a recurrence is not significantly different from

the danger in the initial attack and may, perhaps, be somewhat less. It will be interesting to see how these suggestions are borne out in the larger and more accurately recorded groups of cases which had their onsets in years subsequent to 1907.

In 1908 there were twenty recorded incident pellagrins, of whom two died in the year of onset. The subsequent behavior of the eighteen survivors is shown in detail in Figure 5, and is summarized in Table 4. In this group of cases the ratio of pellagrins with recurrence to pellagrins without recurrence also shows a diminution in the later years. Thus, in 1909 the ratio was 7 to 1; in 1912 it was 3 to 1, and in 1914 less than 2 to 1. The deaths in recurrent attack for this group were only four in fifty-nine recurrent attacks, a death rate of 6.8 per cent., again somewhat lower than the death rate in initial attack for the same group, namely, 10 per cent.

TABLE 4.—Subsequent History up to 1914 of the Eighteen Pellagrins Who Survived an Initial Attack of Pellagra in 1908

	1909	1910	1911	1912	1913	1914	Totals
Pellagrins with recurrence	14	10	11	9	8	7	59
Deaths in year of recurrence	2	0	2	0	0	0	4
Pellagrins living without recurrence	2	4	3	3	4	4	20
Pellagrins dying without recurrence	0	1	0	0	0	0	1
Pellagrins without definite record	2	1	1	1	1	2	8
Pellagrins alive at end of the year	16	15	13	13	13	13	..
Pellagrins considered in the year	18	16	15	13	13	13	..

In 1909 there were fifty-seven recorded incident cases of pellagra with sixteen deaths in the year of initial attack, a rate of 28.1 per cent. The subsequent fate of the forty-one survivors is shown in detail in Figure 6 and is summarized in Table 5. In the following five years there were in this group eighty-four recurrences, a year with one recurrence or with several recurrences being counted as a unit recurrence. There were fourteen deaths in recurrence, the indicated death rate being 16.7 per cent., again less than the death rate in initial attack for the same group. In 1913 and 1914 there were no deaths recorded in this group. The ratio of pellagrins with recurrence to pellagrins who escaped recurrence also shows a progressive diminution in the later years. This ratio was nearly 5 to 1 in 1910; exactly 4 to 1 in 1911; a little more than 2 to 1 in 1912; less than 1 to 1 in 1913 and a little more than 1 to 2 in 1914.

In 1910 there were 141 recorded incident cases of pellagra with twenty-eight deaths in the year of initial attack. The indicated death rate in the year of onset was, therefore, 19.9 per cent. The subsequent

fate of the 113 survivors is shown in detail in Figure 7 and is summarized in Table 6. In this group of pellagrins there were during the four years from 1911 to 1914, 214 recurrences with thirty-one deaths during the year of recurrent attack, a mortality rate of 14.5 per cent. in recurrent attack. The mortality in recurrent attack seems to have diminished progressively in the later years. Of the eighty-eight pellagrins of this group with recurrence in 1911, no less than sixteen died, a mortality of 18.2 per cent. The mortality in 1912 was 15 per cent.; in 1913 it was 12.2 per cent. and in 1914 it was 4 per cent., again suggesting that prognosis as to life in a given attack of pellagra is better the longer the patient has suffered from the disease. The ratio between pellagrins with recurrence and pellagrins who escaped recurrence in each year shows also in this group a progressive diminution in the later years, from about 5 to 1 in 1911 to 2 to 1 in 1912, 1.3 to 1 in 1913 and 0.76 to 1 in 1914.

TABLE 5.—Subsequent History up to 1914 of the Forty-One Pellagrins Who Survived an Initial Attack of Pellagra in 1909

	1910	1911	1912	1913	1914	Totals
Pellagrins with recurrence	29	24	16	8	7	84
Deaths in year of recurrence	4	7	3	0	0	14
Pellagrins living without recurrence	6	6	7	10	13	42
Pellagrins dying without recurrence	2	1	0	0	0	3
Pellagrins without definite record	4	4	4	6	4	22
Pellagrins alive at end of the year	35	27	24	24	24	..
Pellagrins considered in the year	41	35	27	24	24	..

TABLE 6.—Subsequent History up to 1914 of the 113 Pellagrins Who Survived an Initial Attack of Pellagra in 1910

	1911	1912	1913	1914	Totals
Pellagrins with recurrence	88	60	41	25	214
Deaths in year of recurrence	16	9	5	1	31
Pellagrins living without recurrence	17	26	31	33	107
Pellagrins dying without recurrence	3	1	2	1	7
Pellagrins without definite record	5	7	10	18	40
Pellagrins alive at end of the year	94	84	77	75	...
Pellagrins considered in the year	113	94	84	77	...

In 1911 there were 234 recorded incident attacks of pellagra with thirty-three deaths in the year of initial attack. The indicated mortality in the year of onset was therefore 14.1 per cent. The subsequent fate of the 201 survivors in this group is shown in detail in Figure 8 and is summarized in Table 7. In this group of pellagrins there occurred in the three years 258 recurrences with thirty-seven deaths, the indicated death rate in year of a recurrence being, therefore, 14.3 per cent., slightly higher than the mortality during year of onset in this group. Of the 130 pellagrins with recurrence in 1912, there were twenty-one who died during that recurrence, giving a death rate of 16.2 per cent. In 1913 the death rate in recurrence in this group fell to 12 per cent. and in 1914 it was 13.2 per cent. The ratio of pellagrins with recurrence to pellagrins who escaped recurrence during the year again shows a progressive diminution with the lapse of time, being about 2.5 to 1 in 1912, approximately 1 to 1 in 1913 and 0.65 to 1 in 1914.

In 1912 there were 211 recorded incident pellagrins with twenty-seven deaths in initial attack, giving a death rate of 12.8 per cent. in the year of onset; and in 1913 there were 252 recorded incident pellagrins with thirty-eight deaths in the year of onset, giving a death rate in the year of first attack of 15.1 per cent. The subsequent observations on the 184 survivors of the initial attack in 1912 and on the 214 survivors of the initial attack in 1913 are shown in detail in Figure 9 and are summarized in Table 8. Of the 184 survivors of initial attack in 1912, there were ninety-four with recurrence in 1913 and fifty-six with recurrence in 1914. The sum of these recurrences is 150, with 18 deaths, 12 per cent., almost the same as the death rate in the initial attack of the same group. Of the ninety-four recurrences in 1913, death occurred in twelve, or 12.8 per cent., and there were six deaths in the fifty-six recurrences in 1914, or 10.7 per cent. The ratio of pellagrins with recurrence to pellagrins living without recurrence was about 1.5 to 1 in 1913 and approximately 0.9 to 1 in 1914. The 1914 recurrences observed in the 214 survivors with onset in 1913 numbered ninety-five, with four deaths, or 4.2 per cent. The ratio of pellagrins with recurrence to pellagrins without recurrence was very nearly 1.5 to 1. The sum total of all these instances of observations in years subsequent to that of the initial attack is shown in Table 9.

Leaving out the 315 instances of uncertain record and the thirty-five instances of death without recurrence, we have 1,670 instances in which definite information is available concerning a pellagrin in a year subsequent to recovery from the initial attack. In 1,053 of these 1,670 instances, or 63.1 per cent., the record shows recurrence of the disease during the year, and in 617 instances, or 36.9 per cent., there was free-

dom from recurrence. For the whole pellagrous population of Spartanburg County, after recovery from the initial attack, the chance of freedom from recurrence in a given subsequent year was a little better than 1 in 3.

In the 1,053 recurrent attacks there occurred 130 deaths. The general death rate in recurrences was therefore 12.3 per cent., somewhat lower than the general death rate in year of initial attack.

TABLE 7.—SUBSEQUENT HISTORY UP TO 1914 OF THE 201 PELLAGRINS WHO SURVIVED AN INITIAL ATTACK OF PELLAGRA IN 1911

	1912	1913	1914	Totals
Pellagrins with recurrence	130	75	53	258
Deaths in year of recurrence	21	9	7	37
Pellagrins living without recurrence	51	73	82	206
Pellagrins dying without recurrence	2	3	1	6
Pellagrins without definite record	18	27	30	75
Pellagrins alive at end of the year	178	166	158	...
Pellagrins considered in the year	201	178	166	...

TABLE 8.—SUBSEQUENT HISTORY UP TO 1914 OF THE 184 PELLAGRINS WHO SURVIVED AN INITIAL ATTACK IN 1912 AND OF THE 214 WHO SURVIVED AN INITIAL ATTACK IN 1913

	Incident in 1912			Incident in 1913
	1913	1914	Totals	1914
Pellagrins with recurrence	94	56	150	95
Deaths in year of recurrence	12	6	18	4
Pellagrins living without recurrence	60	65	125	62
Pellagrins dying without recurrence	6	2	8	5
Pellagrins without definite record	24	43	67	51
Pellagrins alive at end of the year	166	158	...	203
Pellagrins considered in the year	184	166	...	214

THE FATE OF SURVIVING PELLAGRINS AS INFLUENCED BY THE DURATION OF THE DISEASE

In the preceding examination of the subsequent history of pellagrins incident in each year it has appeared that recurrence was more common in the second year of the disease and that the tendency to recurrence diminished in the later years. There has also seemed to be an indication of a lower death rate in the later years. It therefore appears

to be worth while to rearrange the data in such a way as to make clearer the nature of these relationships.

The behavior in the second year of all those who survived the year of onset is summarized in Table 10 for each annual group of new cases after 1907, and those with onset before 1908 are considered as a single group. Of the 814 pellagrins with onset before 1914 who survived the year of initial attack, there are 114 for whom the record in the second year of the disease is indefinite or uncertain and nineteen who died in the second year without recurrence of the erythema. There remain 681 patients, of whom 482, or 70.8 per cent., showed a recurrent attack in the year following the onset, and 199, or 29.2 per cent., survived the second year without recurrence of pellagra. In this series of

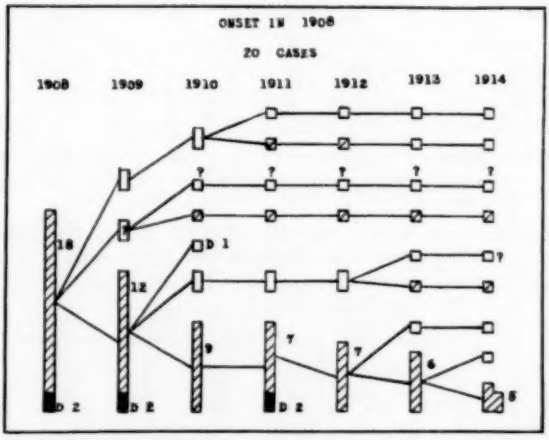


Fig. 5.—Behavior during subsequent years of pellagrins with onset in 1908. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

pellagrins, therefore, there were approximately three in every ten survivors of the initial attack who escaped recurrence in the next year. The proportion of pellagrins with recurrence in the second year is higher than for the average of all years subsequent to the year of onset, for which the rate, as has been shown, was 63.1 per cent. Of the 482 pellagrins with recurrence in the second year of the disease, sixty-three died during that year, the death rate in the first recurrence, that is, in the second year of the disease, being, therefore, 13.1 per cent., somewhat lower than the death rate in year of onset for the whole 1,180 pellagrins, namely, 15.8 per cent., and lower than the death rate in year of onset for the 971 pellagrins incident previous to 1914, namely, 16.2 per cent. (971 cases, 157 deaths), but slightly higher than the gen-

eral death rate for all recurrences, which, as has been shown, was 12.3 per cent.

Of the 482 pellagrins with recurrence in the second year, there were 419 who survived it. Of these 419, there were ninety-one with first recurrence in 1914, so that further records are not available for them. The behavior of the other 328 during the third year of the disease is

TABLE 9.—SUMMARY OF BEHAVIOR IN SUBSEQUENT YEARS OF THE 824 PELLAGRINS WHO SURVIVED AN INITIAL ATTACK PREVIOUS TO 1914

	Year of Incidence							
	Before 1908, Totals	1908	1909	1910	1911	1912	1913	Totals
With recurrence	193	59	84	214	258	150	95	1,053
Deaths in recurrence	22	4	14	31	37	18	4	130
Living without recurrence	55	20	42	107	206	125	62	617
Dying without recurrence	5	1	3	7	6	8	5	35
Without definite record	52	8	22	40	75	67	51	315
Total case-years in the group	305	88	151	368	545	350	213	2,020

TABLE 10.—BEHAVIOR DURING THE SECOND YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED THE FIRST YEAR

Year of Onset	Survivors	Recurrences in Second Year	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	44	32	4	1	1	10
1908	18	14	2	2	0	2
1909	41	29	4	6	2	4
1910	113	88	16	17	3	5
1911	201*	130	21	51	2	18*
1912	184	94	12	60	6	24
1913	213	95	4	62	5	51
Totals	814*	482	63	199	19	114*

* Including one white child, sex unknown.

summarized in Table 11. Of these 328 pellagrins, 228 had a recurrence again in the third year, twenty-nine with fatal termination; sixty-four survived the third year without recurrence, seven died without recurrence, and for twenty-nine of the cases the record is uncertain as regards recurrence. After subtracting the twenty-nine with indefinite record and the seven who died without recurrence, there remain 292

with definite record in regard to recurrence in the third year. Of these, 228, or 78.1 per cent., suffered a recurrence in the third year and sixty-three, or 21.9 per cent., lived through the third year without recurrence. This indicates that those who recover from a recurrence in the second year of the disease are somewhat more liable to recurrence the next year than are those who are just recovering from their initial attack. Of the 228 pellagrins with consecutive attacks to the third year of the disease, twenty-nine died in recurrence in this third year, a mortality rate in the second consecutive recurrence amounting to 12.7 per cent., which is slightly lower than the mortality in recurrent attacks of the second year discussed above.

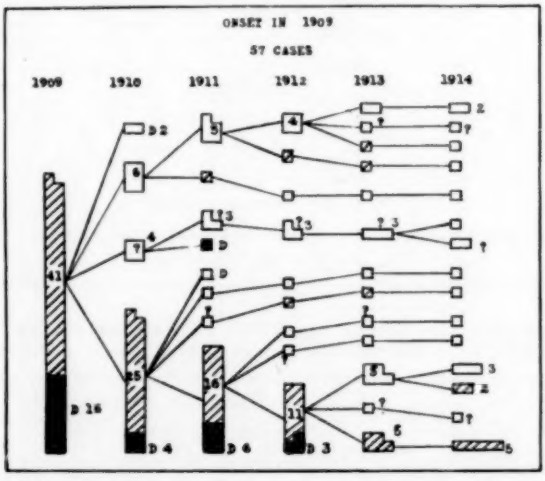


Fig. 6.—Behavior during subsequent years of pellagrins with onset in 1909. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

Of the 199 pellagrins who escaped recurrence during the second year (Table 10), sixty-two had their onset in 1913 and notes for the third year are not available for these. The behavior of the other 137 of this group is summarized in Table 12. Of these 137 pellagrins who escaped recurrence in the second year, fifteen are without definite record for their third year. There remain 122 whose behavior in the third year is definitely recorded. Of these, sixteen suffered a recurrence in the third year, 13.1 per cent. of the 122. The other 106, or 86.9 per cent., escaped recurrence in the third year. Of the sixteen who had a recurrent attack, one died, 6.3 per cent. These figures indicate that absence of recurrent attack in the second year of the disease has not guaranteed freedom from recurrence the following year, but

that, nevertheless, the chance of recurrence in the third year has been very much reduced for this group as compared with those pellagrins with recurrence in the second year (Table 11). In that group a recurrent attack appeared in 78.1 per cent., and only 21.9 per cent. escaped in the third year, while in this group 86.9 per cent. escaped in the third year.

TABLE 11.—BEHAVIOR DURING THE THIRD YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED A RECURRENCE IN THE SECOND YEAR

Year of Onset	Survivors of Recurrence in Second Year	Behavior in Third Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	28	28	1	0	0	0
1908	12	9	0	2	1	0
1909	25	22	6	1	1	1
1910	72	56	8	12	1	3
1911	109	66	8	29	3	11
1912	82	47	6	20	1	14
Totals	328	228	29	64	7	+29

TABLE 12.—BEHAVIOR DURING THE THIRD YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED THE SECOND YEAR WITHOUT A RECURRENCE

Year of Onset	Survivors of Second Year without Recurrence	Behavior in Third Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	1	0	0	1	0	0
1908	2	0	0	2	0	0
1909	6	1	0	5	0	0
1910	17	3	1	14	0	0
1911	51	6	0	41	0	4
1912	60	6	0	43	0	11
Totals	137	16	1	106	0	15

In the second year there were 114 pellagrins without definite record, of whom fifty-seven had their initial attack in 1913 and are therefore without any available record for the third year. The behavior during the third year of the remaining sixty-three is summarized in Table 13. The figures of this table have little significance except to show that

a year of indefinite symptoms was sometimes followed by a frank recurrence and sometimes by a year of good health. Most of the patients in this group continued to have uncertain records, because they could not be seen personally and the information obtained seemed to us too unreliable to warrant a definite decision concerning recurrence or its absence.

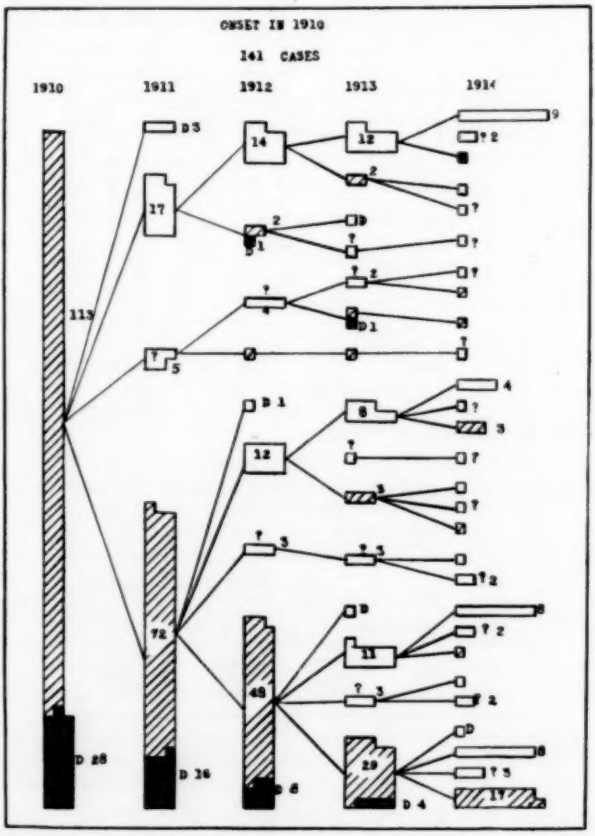


Fig. 7.—Behavior during subsequent years of pellagrins with onset in 1910. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

When we come to a consideration of the events of the fourth year of the disease on this same plan, we are confronted with the necessity of considering nine distinct groups of survivors of the third year, namely, (1) those who had recurrence in the second year and also recurrence in the third year; (2) those with recurrence in the second

year, but no recurrence in the third year; (3) those with recurrence in the second year and an indefinite record in the third year; (4) those without recurrence in the second year and with recurrence in the third year; (5) those without recurrence in the second year and without recurrence in the third year; (6) those without recurrence in the second

TABLE 13.—BEHAVIOR DURING THE THIRD YEAR OF THE DISEASE OF THOSE PELLAGRINS WITHOUT DEFINITE RECORD IN THE SECOND YEAR

Year of Onset	Pellagrins without Definite Record in Second Year	Behavior in the Third Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	10	0	0	0	0	10
1908	2	1	0	0	0	1
1909	4	1	1	0	0	3
1910	5	1	0	0	0	4
1911	18*	3	1	3	0	12*
1912	24	3	0	2	1	18
Totals	63*	9	2	5	1	45*

* Including one white child, sex unknown.

TABLE 14.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED RECURRENT ATTACKS IN THE SECOND AND THIRD YEARS

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	27	23	2	3	0	1
1908	9	9	2	0	0	0
1909	16	14	3	1	0	1
1910	48	33	4	11	1	3
1911	56	35	4	16	1	6
Totals	156	114	15	31	2	11

year and without definite record in the third year; (7) those without definite record in the second year and with recurrence in the third year; (8) those without definite record in the second year and free from recurrence in the third year; (9) those without definite record in the second year and without definite record in the third year. Only the

groups numbered (1), (2), (4) and (5), above, seem to be of sufficient value to warrant their separate consideration. We shall consider each of them separately and group together into one table all the remaining cases which have an indefinite record in either the second or third year or both. All of the patients to be considered in the fourth year had their first attack in the year 1911 or before.

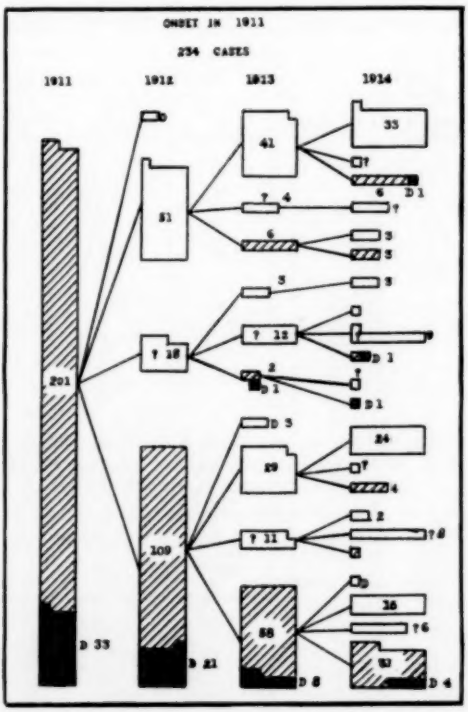


Fig. 8.—Behavior during subsequent years of pellagrins with onset in 1911. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

As has been shown in Table 11, there were 228 pellagrins with recurrence in both the second and the third year of the disease. Of these, twenty-nine died in the third year, leaving 199 survivors. After subtracting the forty-one with onset in 1912, there remain 158 patients in this group for consideration in the fourth year of pellagra. Their behavior in this year is shown in summarized form in Table 14. Of the 158 patients, 114 had recurrence of pellagra in the fourth year, fifteen of these dying; thirty-one escaped recurrence; two died without recurrence and for eleven the record is indefinite. After subtracting

the two who died without recurrence and the eleven with uncertain record, there remain 145 cases for consideration in respect to recurrence. Of these, 114 had recurrence, 78.6 per cent., and thirty-one, or 21.4 per cent., escaped recurrence. The deaths in the fourth consecutive annual attack numbered fifteen in 114 pellagrins who suffered this

TABLE 15.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO HAD RECURRENCE IN THE SECOND YEAR AND SURVIVED WITHOUT RECURRENCE IN THE THIRD YEAR

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	0	0	0	0	0	0
1908	2	0	0	2	0	0
1909	1	0	0	1	0	0
1910	12	3	0	8	0	1
1911	29	4	0	24	0	1
Totals	44	7	0	35	0	2

TABLE 16.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO ESCAPED RECURRENCE IN THE SECOND YEAR AND SURVIVED A RECURRENCE IN THE THIRD YEAR

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	0	0	0	0	0	0
1908	0	0	0	0	0	0
1909	1	0	0	1	0	0
1910	2	0	0	0	1	1
1911	6	3	0	3	0	0
Totals	9	3	0	4	1	1

attack, the indicated mortality rate being 13.2 per cent. higher than has been observed in the recurrences in earlier years of the disease. However, these cases all arose previous to 1912, which fact may require consideration before making too strict comparisons.

As shown in Table 11, there were sixty-three pellagrins who had a recurrence of pellagra in the second year and survived without recur-

rence in the third year. Of these, nineteen had their first attack in 1912 and cannot be considered during the fourth year of their disease. The behavior of the remaining forty-four during the fourth year is summarized in Table 15. Of these forty-four pellagrins two are without definite record in the fourth year. Of the other forty-two, there were seven, or 16.7 per cent., with recurrence of the disease and thirty-five, or 83.3 per cent., without recurrence in the fourth year. There were no deaths from pellagra in this entire group during the fourth year.

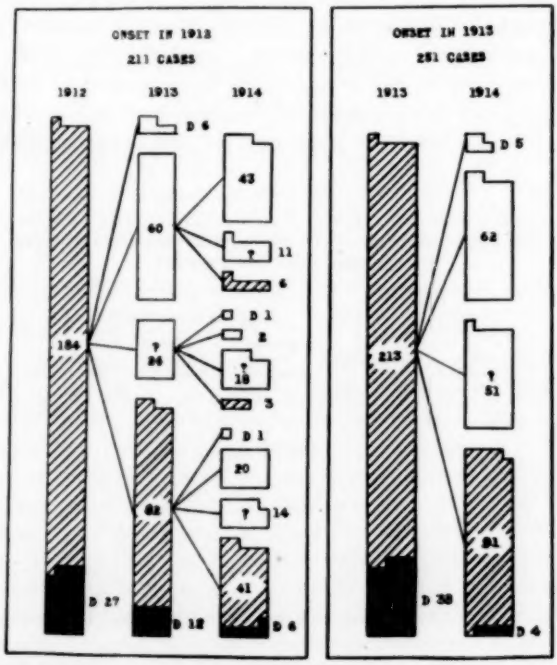


Fig. 9.—Behavior during subsequent years of pellagrins with onset in 1912 and 1913. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

Those pellagrins who survived the second year of the disease without recurrent attack were further subdivided in Table 12, according to their behavior in the third year; fifteen of them had suffered recurrence in the third year. For nine of the fifteen there are records for a fourth year. The behavior of these nine pellagrins during the fourth year is summarized in Table 16. Of these nine patients, one, Pellagrin 9, a white woman, died April 2, 1913, at the age of 34, without recurrence of pellagra in that year. One, a colored woman, has an uncertain

record for the fourth year. Of the remaining seven patients, three, or 42.9 per cent., suffered recurrence in the fourth year and four, or 57.1 per cent., survived the year without recurrence. There were no deaths among the recurrent cases.

The subsequent behavior of this group may be disposed of here at once, because the number of individuals is too small to warrant further tabulation. Of the eight survivors, six had their initial attack in 1911 and records of their further behavior are not available for this study. Of the other two patients, one, Pellagrin 234, a colored woman, with uncertain record in the fourth year, has an uncertain record in the fifth year also and nothing further; the other patient, Pellagrin 80, a white woman, with onset in 1909 at age of 26, no recurrence in 1910, recurrence in 1911 and no recurrence in 1912, remained well and free from recurrence in the fifth and sixth years of her disease, namely, 1913 and 1914.

TABLE 17.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED THE SECOND AND THIRD YEARS WITHOUT ANY RECURRENCE

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	1	0	0	1	0	0
1908	2	1	0	1	0	0
1909	5	1	0	4	0	0
1910	14	2	0	12	0	0
1911	41	7	1	33	0	1
Totals	63	11	1	51	0	1

The 106 pellagrins who survived the third year without having any recurrence in either the second or the third year (Table 12) are of peculiar interest. Does an interval of two years without symptoms warrant the conclusion that the patient has recovered from pellagra? The subsequent behavior of this group has a bearing on this question. Of the 106 pellagrins, there were forty-three with initial attack in 1912, the record of whose behavior in the fourth year of pellagra is not available for this study. The behavior of the remaining sixty-three is summarized in Table 17. One of the patients had an indefinite record in the fourth year. Of the remaining 62, there were fifty-one, or 82.3 per cent., who survived the fourth year also without recurrence, and

eleven pellagrins, 17.7 per cent. of the sixty-two, who suffered recurrence in the fourth year after an interval of two years without definite symptoms of pellagra. It may be of interest to note here that all the eleven patients of this group who had recurrence of the disease in the fourth year were white women. There was one death among the eleven pellagrins with recurrence, 9.1 per cent.

TABLE 18.—Comparative Behavior During the Fourth Year of the Four Groups of Pellagrins Considered in Tables 14, 15, 16 and 17

Table Reference	Previous History of Patients	Behavior in the Fourth Year		
		Recurrences, per Cent.	Deaths in Recurrence, per Cent.	Survivors without Recurrence, per Cent.
14	Recurrences in both second and third years	78.6	13.2	21.4
15	Recurrence in second year; no recurrence in third	16.7	0.0	83.3
16	No recurrence in second year; recurrence in third	42.9	0.0	57.1
17	No recurrence in either second or third year	17.7	9.1	82.3

The comparative behavior of the four groups of pellagrins considered in Tables 14, 15, 16 and 17 is summarized on the basis of percentage in Table 18. This table indicates very definitely that absence of a recurrence in any year is a sign of much better prognosis as far as life is concerned during subsequent years. It also indicates that an absence of recurrence in one year improves very much the prognosis in respect to freedom from the disease in the following year. In the groups shown in Tables 15 and 16 the patients with good health in the fourth year were 83.3 and 82.3 per cent., respectively, about the same proportion of escapes from recurrence as was shown during the third year by those who escaped recurrence in the second year (Table 12), for whom the analogous figure was 86.9 per cent.

In order to complete the consideration of all this series of pellagrins during the fourth year, there is presented in Table 19 a summary of the behavior of those patients for whom the record was indefinite in either the second or the third year or in both. This group includes the twenty-nine patients without definite record from Table 11, the analogous fifteen patients from Table 12 and all the sixty survivors from Table 13. The group is diminished by the loss of those with initial attack in 1912, because their history during the fourth year is not available, and as a result there remain only fifteen in the lot from Table 11, four from Table 12 and thirty-seven from Table 13, a total

of fifty-six cases. Of these fifty-six cases, there were thirty-nine with uncertain record in the fourth year, ten with recurrences and six survivors without recurrence in the fourth year; four died in recurrent attacks and one died without recurrence. The table shows how frequently a year with indefinite or uncertain record was followed by one in which there was a frank attack of pellagra or definite freedom from symptoms. Of course, most of the patients in this group gave very uncertain and indefinite histories for several years in succession.

The number of pellagrins remaining for consideration in the fifth year of the disease is rather small, and when grouped according to their behavior in preceding years, a considerable number of groups require consideration. The more important of these groups will be tabulated.

TABLE 19.—Behavior During the Fourth Year of the Disease of Those Surviving Pellagrins Whose Record Was Indefinite in Any Preceding Year

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	10	1	1	0	1	8
1908	2	1	0	0	0	1
1909	4	1	0	0	0	3
1910	8	3	1	0	0	5
1911	32*	4	2	6	0	22*
Totals	56*	10	4	6	1	39*

* Including one white child, sex unknown.

By referring to Table 14 it will be seen that 114 pellagrins had definite attacks of pellagra in four consecutive years. Of these, fifteen died in the fourth year. Of the remaining ninety-nine, there were thirty-one with onset in 1911, for whom data in regard to the fifth year are not available. There remain only sixty-eight of this group for consideration. Their behavior during the fifth year of the disease is summarized in Table 20. As is shown in the table, four of the sixty-eight were without definite record during the fifth year and one died without recurrence. Of the remaining sixty-three, there were forty-eight, or 76.2 per cent., who had recurrence in the fifth year and fifteen, or 23.8 per cent., survived without recurrence. Among the forty-eight with recurrent attack, there were four deaths, 8.3 per cent., which is the lowest mortality rate so far in this series of cases with annual recurrence of pellagra.

The patients who had recurrences in the second and third years, but survived the fourth year without recurrence, numbered thirty-one. Only fifteen of these can be considered in the fifth year because the other sixteen had their initial attacks in 1911. The behavior of these fifteen pellagrins during the fifth year is summarized in Table 21. Of the fifteen patients, three have an indefinite record for the fifth year, one had a recurrence and eleven survived without recurrence. There were two negro women in this group; one of them had a recurrence and the other an indefinite record for the fifth year. Of the nine white pellagrins, five female and four male, one woman had an indefinite record in the fifth year and the remaining eight survived without recurrence in that year. The figures are small, but they indicate a very good

TABLE 20.—Behavior During the Fifth Year of the Disease of Those Pellagrins Who Survived Annual Attacks of Pellagra for the First Four Years

Year of Onset	Pellagrins in This Category	Behavior During the Fifth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	21	19	4	2	0	0
1908	7	7	0	0	0	0
1909	11	5	0	5	0	1
1910	29	17	0	8	1	3
Totals	68	48	4	15	1	4

prognosis for patients who experience a year without recurrence after having suffered three consecutive annual attacks of pellagra. Of the twelve patients with definite record, one, or 8.3 per cent., had recurrence and eleven, or 91.7 per cent., escaped recurrence. There were no deaths in this group in the fifth year.

The subsequent history of these patients to the end of 1914 will be considered here, inasmuch as they are so few. For the cases incident in 1910 the fifth year ends the history and there are only four others. One of these, Pellagrin 124, a white woman, with onset in 1909, recurrence in 1910 and 1911, no recurrence in 1912 and indefinite record in 1913 (the fifth year), survived the sixth year, 1914, without recurrence. Another, Pellagrin 781, a white man, with onset in 1906, recurrence in 1907 and 1908 and no recurrence in 1909 and 1910 (the fifth year), survived without any further recurrence of the disease to the end of 1914, the ninth year of his disease. A third case, Pellagrin 633, a white man, with onset in 1900, recurrences in 1901 and 1902, no recurrence in 1903 and 1904 (the fifth year), remained free from recurrence also

in 1905, 1906, 1907, 1908 and 1909, had recurrences in 1910 (the eleventh year of the disease), 1911 and 1912, and survived without recurrence in 1913 and 1914 (the fifteenth year of his disease). This patient was an inmate of a hospital for the insane in 1912 and part of 1913. The fourth patient in this residual group, Pellagrin 533, a white woman, with onset in 1893, recurrence in 1894 and 1895, no recurrence in 1896 and 1897 (the fifth year), remained free from recurrence until 1913 (the twenty-first anniversary of her initial attack), the interval of good health being eighteen years. In 1913 she had a recurrence and she survived without recurrence in 1914. This patient was seen in August, 1915, at which time she was still in good health and had experienced no further return of the disease. The significance of these observations will be considered in a subsequent part of this paper.

TABLE 21.—Behavior During the Fifth Year of the Disease of Those Pellagrins Who Had Recurrent Attacks in the Second and Third Years and Survived without Recurrence in the Fourth Year

Year of Onset	Pellagrins in This Category	Behavior During the Fifth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	3	0	0	3	0	0
1908	0	0	0	0	0	0
1909	1	0	0	0	0	1
1910	11	1	0	8	0	2
Totals	15	1	0	11	0	3

Reference to Table 15 will show that seven pellagrins survived a recurrence in the fourth year, after having a recurrence in the second year and no recurrence in the third. Only three of these seven patients had their initial attacks before 1911 and these three had their onset in 1910. One of them, Pellagrin 201, a white woman, has an indefinite record in 1914, the fifth year of her disease. Another, Pellagrin 112, a white woman, remained free from recurrence in 1914. The third, Pellagrin 282, a white woman, had a recurrence in 1914.

Table 15 also shows thirty-five pellagrins surviving the fourth year without recurrence, after recurrence in the second year and no recurrence in the third. Only eleven of these patients had their initial attacks before 1911 and eight of these arose in 1910. One of the eight, Pellagrin 131, a white man, is without definite record in 1914, the fifth

year. The other seven were white women; three of them had recurrences in the fifth year (1914) and four survived without recurrence. Of the three cases with onset previous to 1910, one, Pellagrin 643, a white woman, with onset in 1909, survived without recurrence in 1913 and 1914, the fifth and sixth years of her disease. The two others, Pellagrins 200 and 432, both white women, had their initial attacks in 1908. The former survived without recurrence in 1912 and 1913 and her record for 1914 (the seventh year of her disease) is uncertain. The latter, Pellagrin 432, had no recurrence in 1912 (the fifth year), but suffered a recurrence in May, 1913, within a few days after childbirth, and also had a recurrence in 1914. Of the ten cases with definite record in the fifth year, three, or 30 per cent., had recurrence and seven, or 70 per cent., survived without recurrence. There were no deaths recorded in this group.

TABLE 22.—Behavior During the Fifth Year of Those Surviving Pellagrins Whose Record Was Indefinite in Any Preceding Year

Year of Onset	Pellagrins in This Category	Behavior During the Fifth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	9	2	1	0	0	7
1908	2	1	0	0	0	1
1909	5	1	0	1	0	3
1910	12	2	0	2	0	8
Totals	28	6	1	3	0	19

The survivors after the fourth year of the group of pellagrins with no recurrence in the second year, but with recurrence in the third year, have been discussed in detail in the text in connection with Table 16 (see page 360).

Reference to Table 17 shows eleven pellagrins who survived a recurrent attack in the fourth year, after freedom from symptoms during the second and third years. All were white women. Only four of them had the initial attack previous to 1911. One of these, Pellagrin 654, with onset in 1910, was free from recurrence in the fifth year of the disease, 1914. Another, Pellagrin 544, with onset in 1910, was without definite record in 1914. A third, Pellagrin 178, with onset in 1909, suffered a recurrence in 1913 (the fifth year), but escaped recurrence in 1914, being pregnant during the spring and summer. The fourth patient, Pellagrin 166, with onset in 1908, suffered a recurrent

attack in the fifth year, 1912, but survived without recurrence in 1913 and 1914, the sixth and seventh years of the disease.

In Table 17 there were fifty-one survivors of the fourth year without any recurrence after the year of onset. Of these, eighteen had the initial attack previous to 1911, so that further history is available. Nine of them were white women with onset in 1910; of these, seven were without recurrence in the fifth year (1914) and one, Pellagrin 860, suffered a recurrence early in 1914 (the fifth year), about five weeks

TABLE 23.—Comparative Behavior During the Fifth Year of the 115 Pellagrins with Definite Record in the Fifth Year, Grouped According to Their Record in Preceding Years

Table Reference	Recurrences in Previous Years			Number of Cases	Recurrences		Deaths		Living without Recurrence	
	2d	3d	4th		Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
20	+	+	+	63	48	76.2	4	8.3	15	23.8
21	+	+	0	12	1	8.3	0	0.0	11	91.7
	+	0	+	2	1	50.0	0	0.0	1	50.0
	+	0	0	10	3	30.0	0	0.0	7	70.0
	0	+	+	0	0	....	0	....	0	....
	0	+	0	1	0	0.0	0	0.0	1	100.0
	0	0	+	3	2	66.7	0	0.0	1	33.3
	0	0	0	15	2	13.3	1	50.0	13	86.7
Total, history definite.....	..	..	..	106	57	53.8	5	8.8	49	46.2
Indefinite in any year (22)	..	..	..	9	6	66.7	1	16.7	3	33.3
Totals.....	..	..	..	115	63	54.8	6	9.5	52	45.2

before giving birth to a child, and she died of pellagra June 21, 1914. The other patient, Pellagrin 437, was without definite record in 1914. Three of the group of eighteen were white men with onset in 1910, of whom two remained free from recurrence in the fifth year, 1914, and one, Pellagrin 104, was without definite record in that year. Four of the eighteen were white women with onset in 1909, Pellagrins 119, 422, 644 and 817. Pellagrin 119 was without definite record in 1913 and 1914, having moved away. Pellagrins 422 and 817 survived without recurrence in 1913 and 1914, the fifth and sixth years of the disease. Pellagrin 644 suffered a recurrence in the fifth year (1913), but remained free from recurrence in 1914. This last case is an example

of recurrence (or of a second onset?) after three years without symptoms. One of the group of eighteen, Pellagrin 1124, a white woman, had her initial attack in 1908. She escaped recurrence in the fifth, sixth and seventh years of the disease (1912, 1913 and 1914) as well as in the earlier years. This case is possibly a valid example of complete recovery after a single attack of pellagra. The last remaining case in the group, Pellagrin 689, a white woman, had her initial attack in 1905 and remained without recurrence up to and including 1914, the tenth year. This case is another possible example of recovery after one attack. Her history is vouched for by a very reliable physician who has had a large experience with pellagra in Spartanburg County and has had this patient continuously under observation. Of the whole eighteen pellagrins without recurrence to the end of the fourth year, there were three without definite record in the fifth year, two with recurrence, one of which resulted in death, and thirteen without recurrences in the fifth year. Of the fifteen with definite record, thirteen, or 86.7 per cent., continued free from symptoms in the fifth year.

TABLE 24.—Behavior During the Sixth Year of Those Pellagrins Who Survived Annual Attacks of Pellagra for the First Five Years

Year of Onset	Pellagrins in This Category	Behavior During the Sixth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	15	15	0	0	0	0
1908	7	6	0	1	0	0
1909	5	5	0	0	0	0
Totals	27	26	0	1	0	0

By reference to Table 19 it will be seen that fifty-three Pellagrins who had indefinite record for either the second or the third year or both survived the fourth year. Of these, twenty-one had their initial attacks before 1911 and are, therefore, available for consideration in the fifth year of the disease. To these twenty-one may be added six with indefinite record in the fourth year, from Table 14, one from Table 15, one from Table 16 and none from Table 17, making a total of 29 patients with uncertain record in one or more previous years, to be considered in the fifth year of the disease. The behavior of these cases during the fifth year is summarized in Table 22. Twenty of the twenty-nine had indefinite record in the fifth year, six had recurrent attacks, with one death, and three survived the fifth year without recurrence. There were only nine pellagrins of this group with definite

record in the fifth year, 66.7 per cent. of them having recurrence and 33.3 per cent. surviving without recurrence. There was one death among the six with recurrent attacks, 16.7 per cent.

Table 23 shows in summary a comparison of the behavior during the fifth year of the different groups determined by behavior in previous years. Many of the groups are too small for the percentage figures to be significant. The group with annual recurrence in consecutive years includes sixty-three pellagrins and shows a recurrence rate of 76.2 per cent., which is higher than for any other group. The death rate in recurrence in this group was 8.3 per cent., four deaths in forty-eight recurrences, a mortality rate considerably lower than that for the initial attack or for earlier recurrences. Among the forty-three pellagrins who escaped recurrence in one or more of the first four years of the disease (all the remaining groups with definite history) there were only nine recurrent attacks in the fifth year, 20.9 per cent., and only one death, 11.1 per cent. of those with recurrence. For the thirty-eight who escaped recurrence in the fourth year, the prognosis for the fifth year appeared to be particularly good, as only six of them, 15.8 per cent., suffered recurrence in the fifth year.

TABLE 25.—Behavior During the Sixth Year of the Disease of Those Pellagrins Whose Record Was Indefinite in Any Preceding Year

Year of Onset	Pellagrins in This Category	Behavior During the Sixth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	8	3	0	0	1	4
1908	2	1	0	0	0	1
1909	8	0	0	4	0	4
Totals	18	4	0	4	1	9

The only pellagrins in this series whose histories have not already been traced to the end of the record are those included in Tables 20 and 22. In Table 20 there were shown forty-eight pellagrins with recurrent attacks every year up to and including the fifth year of the disease. Of these, forty-four survived the fifth year and for twenty-seven of them the record extends to the sixth year. The behavior of these twenty-seven survivors is summarized in Table 24. In twenty-six of the twenty-seven cases, or 96.3 per cent., the disease recurred in the sixth year, with no deaths, and in one, or 3.7 per cent., there was freedom from recurrence in the sixth year. This one patient, Pellagrin 277, a white woman, also remained free from recurrence in 1914, the

seventh year of her disease. Of the fifteen pellagrins of Table 20, who survived the fifth year without recurrence, seven have further records. Pellagrin 444, a white woman, with onset in 1907, recurrences in 1908, 1909 and 1910 and freedom from recurrence in 1911 (the fifth year), survived without recurrence in 1912 and 1913, the sixth and seventh years, but suffered recurrence in 1914, the eighth year of her disease. Pellagrin 642, a white woman, with onset in 1904, recurrences in 1905, 1906 and 1907 and freedom from recurrence in 1908 (the fifth year), remained free from recurrence through 1913 (the tenth year), but suffered recurrence (or a new onset?) in 1914, the eleventh year of her disease, and died of pellagra in September, 1914. The remaining five of this group were also all white women and their initial attacks occurred in 1909. Pellagrins 94 and 163 suffered recurrence in the

TABLE 26.—Subsequent Behavior of Eight Pellagrins Who Survived the Sixth Year After Having an Indefinite Record in Any Preceding Year

Pellagrin	Onset	Recurrence in Subsequent Years					
		7th	8th	9th	10th	11th	12th
1187	1900	+	?	?	+	+	+ D
298	1903	+	+ D				
285	1903	?	+ D				
774	1904	?	+ D				
1024	1905	+	+	+	+		
70	1905	?	+	+ D			
543	1906	?	?	0			
207	1907	+	?				

sixth year (1914) and Pellagrins 151, 128 and 59 survived the sixth year (1914) without recurrence. In the sixth year, therefore, five, or 71.4 per cent. of the seven, remained free from recurrence and two, or 28.6 per cent., suffered recurrence, with no deaths in the sixth year.

The one surviving pellagrin with indefinite record for the fifth year in Table 20, for whom further record is available, and the fifteen surviving pellagrins of Table 22, with onset before 1910, constitute a group of pellagrins with uncertain record in some one of the first five years, whose subsequent behavior is still to be discussed. To these fifteen cases may be added also Pellagrin 124, with indefinite record in the fifth year (Table 21 and accompanying text), and Pellagrin 119 (discussed on page 366), making eighteen patients in all, with indefinite record in one or more years previous to the sixth. Their behavior in

the sixth year is summarized in Table 25. Of the eighteen pellagrins, nine had an indefinite record in the sixth year and one died without recurrence; eight had definite records, four having recurrences and four surviving without recurrence in the sixth year. There were no deaths in recurrent attacks. The two patients with onset in 1908 in Table 25 were Pellagrin 22, a white man, and Pellagrin 1,229, a white woman. The former had a recurrence again in 1914, the seventh year of his disease, and the latter was again without definite record in the seventh year. The eight surviving patients in this table with onset in years previous to 1908 had their initial attacks in various years. Their behavior after the sixth year to the end of the record is shown in Table 26. In the seventh year three had recurrences and five had indefinite records. In the eighth year five had recurrences, three of them dying, and three had indefinite records. In the ninth year two had recurrences, one dying; one escaped recurrence and one had indefinite record. In the tenth year one had recurrence and the other an indefinite record. This last-mentioned case, Pellagrin 1,187, had recurrences in the eleventh and twelfth years, dying in the latter year. Three of these eight patients remained alive at the end of 1914.

TABLE 27.—BEHAVIOR DURING THE SEVENTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED ANNUAL ATTACKS OF PELLAGRA DURING SIX CONSECUTIVE YEARS

Year of Onset	Pellagrins in This Category	Behavior in the Seventh Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	15	14	1	1	0	0
1908	6	5	0	1	0	0
Totals	21	19	1	2	0	0

In Table 24 there were shown twenty-one pellagrins with onset before 1909 who survived annual attacks of pellagra during six consecutive years. The behavior of these patients during the seventh year of the disease is summarized in Table 27. Of the twenty-one pellagrins, nineteen, or 90.5 per cent., had recurrences in the seventh year and two, or 9.5 per cent., survived without recurrence in this year. There was one death in recurrent attack, indicating a mortality rate of 5.3 per cent. One of those who escaped recurrence, Pellagrin 51, a white woman, had her first attack in 1907. She also escaped recurrence in 1914, the eighth year of her disease. The other twelve sur-

vivors with onset before 1908 had their initial attacks in various years. Their behavior in the later years of the disease up to the end of the record in 1914 is shown in Table 28. Of the twelve patients, nine had recurrences in the eighth year and three had indefinite record. In the ninth year, nine patients remained to be considered. Eight of them had recurrences, one dying, and one had an indefinite record. Of the seven patients remaining for consideration in the tenth year, one died without recurrence, one survived without recurrence and five suffered recurrence. In the eleventh year all of the four patients with available records had recurrence and one of them committed suicide by drowning. Beyond the eleventh year only one pellagrin remained for consideration. He suffered recurrence every year to and including 1912, the twenty-first year of his disease, and died early in 1913 without recurrence in the latter year.

TABLE 28.—Subsequent Behavior of Twelve Pellagrins Who Survived Annual Attacks of Pellagra During Seven Consecutive Years

Pellagrin	Onset	Recurrence in Subsequent Years							
		8th	9th	10th	11th	12th	13th	14th	15th
20	1892	+	+	+	+	+	+	+	+*
286	1898	+	+	+	+†				
354	1901	+	+	‡					
145	1904	+	+	+	+				
996	1904	+	+	+	+				
168	1905	+	+	+					
563	1905	+	+	0					
582	1905	+	+ D						
205	1906	?	?						
445	1907	+							
659	1907	?							
421	1907	?							

* Pellagrin 20 suffered recurrence every year to and including 1912, the twenty-first year of disease. He died Feb.27, 1913, without recurrence in 1913.
† Died, suicide.
‡ Lived without recurrence.

Much as the group of pellagrins with onset before 1908 has been discussed in various places in the preceding pages, the data in regard to the behavior of this group according to the year of the disease are summarized in Table 29 to the end of the fifteenth year. The records of only two cases extend beyond that year. Pellagrin 20, a white man, with onset in 1892, continued to suffer recurrences every year from the sixteenth to the twenty-first year, inclusive, and he died early

in the twenty-second year of the disease, without a recurrence in that year. Pellagrin 533, a white woman, with onset in 1893, continued to be free from recurrence from the sixteenth to the twentieth year, inclusive; she suffered a recurrence in the twenty-first year of her disease (1913) and survived without recurrence the twenty-second year.

TABLE 29.—Behavior of Pellagrins with Onset Before 1908 in the Years Subsequent to the Initial Attack

	Year													
	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Recurrences	32	28	24	21	18	17	15	10	7	7	3	2	1	1
Deaths in recurrence	4	1	3	5	0	1	3	2	0	2	1	0	0	0
Living without recurrence	1	1	4	6	6	7	6	6	5	1	1	1	2	2
Dying without recurrence	1	0	1	0	1	0	0	0	1	0	0	0	0	0
Indefinite record	10	10	0	7	4	4	6	2	0	0	0	0	0	0

COMMENT

From the records of these cases in the successive years of their disease it is possible to draw certain deductions of general application to the prognosis of pellagra. Considering only those with definite records and with a history of attack in each year after onset, we obtain the figures shown in Table 30. One striking feature of these data is the evident increased tendency for recurrence to appear with greater certainty after the habit has become established. The lowest recurrence rate, 70.8 per cent., occurred in the year following the initial attack. From the third to the fifth year the recurrence rate was between 75 and 80 per cent., and after the fifth year it was constantly above 90 per cent. Another important feature is the death rate in recurrence, which is consistently lower than the death rate in initial attack, which was 15.8 per cent. for the entire series of cases. From the second to the fourth year, inclusive, the death rate in recurrence was between 12.5 and 13.5 per cent. After the fourth year it remained consistently below 10 per cent., except where the number of individuals became so small that a single death gave a higher percentage. For all recurrences after the fourth year added together (129) there were only seven deaths, indicating a death rate of 5.4 per cent. for these years. This fact is in direct conflict with the statement commonly made in textbooks that the prognosis in an attack of pellagra is less favorable in the later years of the disease. As far as life is concerned and as far as recovery from that one attack is concerned, the prognosis would appear from

our data to be distinctly better in the later years. On the other hand, the prognosis in respect to freedom from recurrence in subsequent years would appear to be less favorable in the later years for those with consecutive annual recurrences. The improved prognosis in respect to life cannot be ascribed to the increasing age of the patients, because, as we have already shown in a study[2] of a part of these patients, the death rate is higher in older pellagrins in both initial and recurrent attacks.

TABLE 30.—Tendency to Recurrence and Death Rate in Recurrence in Successive Years for Pellagrins with Consecutive Annual Attacks

	Year											
	2	3	4	5	6	7	8	9	10	11	12	13-21
Pellagrins considerde..	681	292	144	63	27	21	9	8	5	4	1	0*
Recurrences.....	482	228	113	48	26	19	9	8	5	4	1	0*
Recurrences, per Cent...	70.8	78.1	78.5	76.2	96.3	90.5	100	100	100	100	100	100
Deaths in recurrence....	63	29	15	4	0	1	0	1	0	1	0	0
Death rate, per Cent....	13.1	12.7	13.3	8.3	0.0	5.3	0.0	12.5	0.0	25.0	0.0	0.0

* Pellagrin 20 continued to have recurrences each year to the twenty-first year. He died in the twenty-second year without recurrence.

Those pellagrins who escaped recurrence every year after the year of onset up to the year of a definite observation serve as a criterion of recovery after a single attack. The rate of recurrence and the death rate among those who had recurrence for the patients in this category are indicated in Table 31. The number of individuals in this category is small, especially after the fifth year of the disease. Up to the fifth year, however, the figures are significant and they indicate very clearly that a person who has had an initial attack of pellagra and then escaped recurrence altogether for one, two or three years has about fifteen chances in a hundred of suffering a recurrence in the next following year. Furthermore it would seem to make very little difference whether the interval without symptoms had been one, two or three years, as the recurrence rate was between 13 and 18 per cent. in all three of these groups.

Those patients who escaped recurrence in a single year after an unbroken series of annual attacks of pellagra may be worthy of special attention also. Thus in the third year there are definite records for 122 pellagrins who had escaped recurrence in the second year. In the fourth year there are definite records for forty-two individuals who suffered an attack in the first year and again in the second, but escaped

2. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Prognosis in Pellagra, Proc. New York Path. Soc., 1915, xv, 30.

recurrence in the third year. What is the effect of this one year's freedom from recurrence on the prognosis for the following year? The data on this question are summarized in Table 32. The number of cases in this category is also quite limited, but for three years there are enough cases to be somewhat significant. Of the 122 patients who escaped recurrence in the second year, sixteen, or 13.1 per cent., had recurrence in the third year. Of the forty-two who had recurrence in the second year and escaped recurrence in the third year, 16.7 per cent. suffered recurrence in the fourth year. Of the twelve patients with

TABLE 31.—TENDENCY TO RECURRENCE AND DEATH RATE IN RECURRENCE IN SUCCESSIVE YEARS FOR PELLAGRINS WITHOUT RECURRENCE FROM YEAR OF ONSET TO YEAR OF OBSERVATION WITH DEFINITE RECORD

	Year of the Disease							
	3	4	5	6	7	8	9	10
Pellagrins considered	122	62	15	4	2	1	1	1
Recurrences	16	11	2	0	0	0	0	0
Recurrences, per cent.	13.1	17.7	13.3	0.0	0.0	0.0	0.0	0.0
Deaths in recurrence	1	1	1	0	0	0	0	0
Death rate, per cent.	6.3	9.1	50.0	..	..	..	..	..

TABLE 32.—TENDENCY TO RECURRENCE AND DEATH RATE IN RECURRENCE IN SUCCESSIVE YEARS OF THE DISEASE FOR PELLAGRINS WHO HAVE HAD ONLY A SINGLE YEAR WITHOUT RECURRENCE IMMEDIATELY PRECEDING THE RESPECTIVE YEAR

	Year of the Disease					
	3	4	5	6	7	8
Pellagrins considered	122	42	12	7	1	1
Recurrences	16	7	1	2	0	0
Recurrences, per cent.	13.1	16.7	8.3	28.6	0	0
Death in recurrence	1	0	0	0	0	0
Death rate, per cent.	6.3	0.0	0.0	0.0	..	..

recurrence in the second and third years, but without recurrence in the fourth year, only one, or 8.3 per cent., suffered recurrence in the fifth year. The prognosis in respect to recurrence has been as good for these patients as for those who had no recurrence at all after the year of onset, shown in Table 31. From both these tables it is evident that freedom from recurrence in a single year renders the prognosis for the next year very good, as more than 80 per cent. of such patients escaped for the next year also. These data do not indicate any better prog-

nosis for those who have escaped recurrence for two or more consecutive years than for those who have escaped for a single year.

In the entire series of cases there were twenty-three patients who suffered recurrence after two or more consecutive years of freedom from recurrence. Four of these had their initial attacks previous to 1908. The other nineteen can be located on the charts. Fourteen of these were instances of recurrence after two years of freedom from attack, five after three years of freedom from attack, two after six years, one after seven years and one after seventeen years without recurrence. Among these twenty-three patients there were four who died in that new recurrent attack, one after two years without recurrence, one after three years without recurrence and two after six years without recurrence. The death rate of 17.8 per cent. (four out of twenty-three) for the group is rather high, indicating a poor prognosis for those pellagrins who suffer recurrence after an interval of several years without erythema.

SUMMARY

1. The total number of recorded recurrent attacks of pellagra in this series of patients was 1,053, with 130 deaths in the year of recurrence. The death rate in recurrence was therefore 12.3 per cent.

2. The total number of instances of freedom from recurrent attack of pellagra during a year numbered 617. The ratio of nonrecurrence to recurrence was therefore 617 to 1,053, or approximately 4 to 7.

3. For pellagrins in the later years of the disease the prognosis is more favorable for recovery from the present attack but apparently less favorable in respect to escape from recurrence in the next subsequent year. In other words, after successive annual attacks the disease seems to become more firmly established as a chronic disease with annual manifestations, but also becomes less acutely malignant.

4. A year without recurrence is a very favorable omen. Subsequent recurrence is less likely to appear and if it does appear it is less likely to end in death.

5. Recurrence after several years of freedom from the disease is not uncommon and a considerable proportion of these recurrences end fatally.

6. It is impossible to say when a patient has definitely recovered from the disease pellagra. It seems to us very much more advisable to speak of recovery from the particular attack of the disease in a given year. In those patients who escape recurrence for one or more years it is best to consider the disease as arrested or as inactive, much as we do in tuberculosis or in syphilis.

THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

WITH INTRAVENOUS SALVARSAN ALONE, WITH INTRAVENOUS SALVARSAN AND INTRASPINAL SALVARSANIZED SERUM TOGETHER AND WITH INTRASPINAL SALVARSANIZED SERUM ALONE *

I. C. WALKER, M.D., AND D. A. HALLER, M.D.
BOSTON

Since Swift and Ellis first published their method of intraspinal treatment with salvarsanized serum for patients with syphilis of the central nervous system, much has been written by many observers both in favor of and against the method of Swift and Ellis. These opposite opinions probably to a certain extent have resulted from the limited amount of experience each observer has had with this treatment, as the majority of reports have been based on a few cases, without using other methods for control. It is obvious that in treating a few cases by the same method one observer might meet only favorable cases, while another observer might meet unfavorable ones. A fairer estimate of the value of the method would seem to be obtained from a large series of variously treated cases which have been carefully followed during treatment and which have been under observation for some time since the treatment was stopped. It is with this in mind that we report in detail on all the cases treated by the three methods, intravenous salvarsan alone, intraspinal salvarsanized serum alone, and both intravenous salvarsan and intraspinal salvarsanized serum, at the Peter Bent Brigham Hospital since its opening three years ago, in order to compare the results following each method.

Seventy-five patients with the following diagnoses have been treated: forty-eight cases of tabes dorsalis, six of general paresis of the insane, sixteen cases of cerebrospinal syphilis, and five of syphilitic meningitis. To these patients 450 intraspinal injections of salvarsanized serum and 350 doses of salvarsan were given. In this paper for means of comparison the cases are grouped according to the way the patients were treated, so that all cases naturally fall into one of the three following groups: in group 1 are those cases in which the patients were treated with intravenous salvarsan alone; in group 2 are those in which the patients were treated with both intravenous salvarsan and

* Submitted for publication, March 20, 1916.
* From the Medical Clinic of the Peter Bent Brigham Hospital.

intraspinal salvarsanized serum; and in group 3 are those cases in which the patients were treated with intraspinal salvarsanized serum only, no other medication being used.

At first all patients with central nervous system syphilis were treated with salvarsan alone; but if, as happened in many cases, four or six injections of salvarsan were not followed by much improvement in the symptoms or by a change in the Wassermann reaction and in the cell count in the spinal fluid, these patients were then given salvarsanized serum intraspinally in conjunction with the intravenous salvarsan. This double method of treatment was followed usually by improvement in both the clinical symptoms and the laboratory findings. Since the intraspinal salvarsanized serum seemed to reinforce salvarsan alone, we desired to determine if there was actually any value in the intraspinal salvarsanized serum itself. We therefore selected patients with negative Wassermann reactions in the blood serum, but with positive findings in the spinal fluid, for intraspinal treatment with salvarsanized serum alone. We felt justified in this procedure, since many patients had not improved under salvarsan alone, and, furthermore, if such treatment should prove to be beneficial, three patients could be treated with one dose of salvarsan, that is, one with salvarsan and two with that patient's serum. Our hopes were realized, for we found that these selected patients improved from every viewpoint following the intraspinal treatment with salvarsanized serum alone. Therefore we have adhered to the following schedule: to patients with a positive reaction in both blood and spinal fluid, first, salvarsan alone is given; if satisfactory improvement does not follow, then salvarsanized serum is given intraspinally in conjunction with salvarvarsan; to those with a negative Wassermann reaction in the blood serum, but with positive findings in the spinal fluid, is given only intraspinal salvarsanized serum.

Drugs other than salvarsan[1] have been used very sparingly in these cases. Neosalvarsan was discontinued in the treatment of all cases of syphilis after a short trial, since the early stages of the disease did not yield to it as readily as to the original salvarsan and what improvement did follow its use was temporary. Mercury in the form of inunctions and intramuscular injections was employed very little because of the frequency of a falsely negative Wassermann reaction following its use. Morphin and aspirin were required in an occasional case to control the temporary reaction pains following intraspinal treatment. Other than the foregoing treatment no therapy was used.

All patients receiving intravenous salvarsan alone and all of those receiving intraspinal salvarsanized serum alone were required to remain

1. Recently diarsenol has been substituted for salvarsan.

in the hospital the night immediately following the treatment, but they were discharged the next morning. Those patients treated with both intravenous salvarsan and intraspinal salvarsanized serum were frequently given both treatments in the same afternoon, so that only one night was spent in the hospital; usually, however, these patients were given salvarsan on one afternoon and intraspinal salvarsanized serum on the next afternoon, in which case these patients remained in the hospital two nights.

During the first year and a half all patients, with some exceptions which will be mentioned, were treated at weekly intervals; but as this seemed to be too frequent in some cases, the interval between treatments was lengthened to three weeks in some patients and to irregular intervals in others. These longer intermissions between treatments were not followed by as rapid improvement as were the weekly periods, so that no definite rule has since been followed. Each case is a rule unto itself, but the best results seemed to follow frequent treatments.

Occasionally a patient experienced a marked reaction for eighteen or twenty hours following the intraspinal treatment, this reaction consisting of a severe aggravation of the pains experienced previous to treatment or a renewal of the pains complained of years previously. Such reactions could be avoided often by increasing the interval between treatments in that particular case. A moderate reaction, consisting of an aggravation of symptoms lasting for a few hours, is to be desired, as more improvement in every way followed than resulted when there was but a slight reaction or none at all. Frequently it is difficult to differentiate the different types of central nervous system syphilis on account of the vague symptoms and the absence of distinctive signs. However, in such cases the reaction following intraspinal treatment will cause an accentuation of indefinite symptoms and will revive forgotten symptoms, which will aid in making a diagnosis. Occasionally, after a severe reaction, the spinal fluid cell count was increased and many red blood cells were present, but if treatment was omitted for two weeks the cell count fell to its previous level, and the red blood cells disappeared.

The technic employed in the preparation of the salvarsanized serum was that described by Swift and Ellis, except that larger doses of intravenous salvarsan were given, these usually being 0.5 gm. and 0.6 gm., and the blood was withdrawn one half hour instead of one hour later; and for the intraspinal injection from 20 c.c. to 25 c.c. of whole serum instead of a 40 or 50 per cent. dilution of the serum with saline was used. These modifications should increase several times the amount of available salvarsan, or whatever it is present in the serum, over that obtained by the original method of Swift and Ellis. These

large amounts of serum withdrawn such a short time after the injection of salvarsan probably contain as much arsenic or salvarsan as has been found safe to inject by itself directly into the meninges.

The benefit from treatment and the indication for the best method of treatment to follow in each case were based on the resultant changes in the patients' symptoms and in the cell count and the Wassermann reaction of the spinal fluid. All observers agree that the Wassermann reaction in the spinal fluid is a dependable test and very resistant to changes by treatment. We have titrated all spinal fluids, using amounts of spinal fluid varying from 2 c.c. to 0.05 c.c. in each tube against a 0.4 per cent. cholesterin reinforced human heart antigen, and we have found that in untreated cases the spinal fluid gave fixation with the same amounts on successive tests and that cases with little treatment showed little or no effect on the intensity of fixation. Other observers agree that patients with central nervous system syphilis are prone to have periods of spontaneous improvement which may or may not be followed by remissions. Consequently, one must be very cautious in interpreting improvement as due to treatment. We have followed our patients with great care, always having in mind spontaneous improvement, and, furthermore, since our patients are under our observation indefinitely after treatment has stopped, we are able to verify or discredit our previous conclusions, so that we feel justified when we state that the patient showed improvement.

Just as there is universal agreement in the reliability and the constancy of a positive Wassermann reaction in the spinal fluid and universal agreement in the unreliability to a certain extent in symptomatic improvement due to treatment, so is there disagreement as to the value, constancy and interpretation of an increased cell count in the spinal fluid. In our cases of syphilitic meningitis the cell count varied from 500 to 9,800, and in one case, which was probably one of meningitis, the cell count was only 150; in these cases the predominating cell was of the small lymphoid variety, with a high percentage of the endothelial type of cell and a small percentage of the polymorphonuclear type. Under treatment the lymphoid type of cell relatively increased and the other types of cell absolutely decreased, thus leaving only the lymphoid cell, which slowly decreased to normal. In our cases of cerebrospinal syphilis, general paresis of the insane and tabes dorsalis the cell counts varied from 10 to 200. In the first two diseases the prevailing type of cell was the large endothelial variety, with a few of the small endothelial and small lymphoid types; under treatment the large endothelial cell rapidly decreased and the small types of cell slowly decreased. In the cases of tabes the small lymphoid cell was usually the only one present; occasionally a few small endothelial cells were noted. However, the number and type of cell were really of

TABLE 1.—Comparison Between the Effect of Treatment with Several Doses of Intravenous Salvarsan and with One Intraspinal Injection of Salvarsanized Serum

Case Number*		Salvarsan in Grams at Weekly Intervals	Change in Cell Count	Change in Wassermann Reaction	Clinical Improvement	Intraspinal Serum, C.c.	Change in Cell Count
T. D.	1	0.4, 0.6, 0.6, 0.6, 0.6, 0.6	44 to 35	None	None	14	35 to 7
	22	0.4, 0.6, 0.6, 0.6, 0.6, 0.6	7 to 7	None	Slight	20	7 to 6
	3	0.3, 0.4, 0.5, 0.6, 0.6, 0.6	2 to 2	None	Slight		
	2	0.3, 0.4, 0.6, 0.6, 0.6, 0.6	6 to 5	None	None		
C. S.	71	0.4, 0.6, 0.6, 0.6, 0.6, 0.6	51 to 7	0.3 c.c. + to 1.5 c.c. ±			
	52	0.4, 0.6, 0.6, 0.6, 0.6, 0.6	98 to 29	0.2 c.c. + to 1 c.c. +	Headache relieved		
	62	0.3, 0.4, 0.4, 0.4, 0.4	42 to 4	None			
T. D.	6	0.4, 0.4, 0.4, 0.4, 0.4	10 to 7	0.3 c.c. + to 0.4 c.c +	None		
C. S.	7	0.3, 0.4, 0.6, 0.6, 0.6	6 to 6	None	Headache relieved		
T. D.	67	0.4, 0.4, 0.6, 0.6, 0.6	15 to 7	None	Slight		
C. S.	72	0.3, 0.6, 0.6, 0.6, 0.6	30 to 27	None	None	16	30 to 10
T. D.	30	0.4, 0.5, 0.6, 0.6	32 to 32	None	None		
M.	37	0.3, 0.5, 0.6, 0.6	940 to 33	0.5 c.c. + to 1 c.c. +	Stiff neck, positive Kernig's relieved		
	23	0.3, 0.4, 0.6	550 to 558	None	Headache relieved	20	533 to 272
T. D.	20	0.3, 0.5, 0.5	16 to 15	None	None	16	15 to 57
C. S.	18	0.3, 0.4, 0.5	80 to 84	None	None	16	84 to 40
	10	0.3, 0.4, 0.6	39 to 47	None	None	18	47 to 55
	45	0.3, 0.5, 0.6	15 to 14	None	None	18	14 to 5
T. D.	28	0.4, 0.5, 0.6	100 to 80	None	None	18	80 to 37
	47	0.3, 0.4, 0.4	80 to 21	None	None	20	21 to 7
	49	0.3, 0.6, 0.6	37 to 64	None	Diplopia relieved	23	64 to 30
C. S.	52	0.4, 0.6, 0.6	98 to 60	0.3 c.c. + to 1 c.c. +	Much improvement		

T. D.	61	0.3, 0.4, 0.4	.....	0.3 c.c. + to 0.4 c.c. +	Slight improvement		
	68	0.3, 0.4, 0.4	.....	None	None		
	69	0.3, 0.4, 0.6	17 to 10	None	None		
	19	0.3, 0.4	12 to 18	None	None	13	18 to 9
G. P. I.	13	0.3, 0.5	19 to 43	None	None	14	43 to 13
T. D.	14	0.3, 0.4	33 to 35	None	None	20	35 to 26
	17	0.3, 0.5	90 to 88	None	None	20	88 to 47
C. S.	50	0.3, 0.5	22 to 28	None	None	23	28 to 20
T. D.	53	0.3, 0.5	16 to 20	None	None	18	20 to 11
	54	0.3, 0.5	72 to 72	None	None	20	72 to 30
	55	0.3, 0.5	17 to 17	None	None	16	17 to 11
	56	0.3, 0.4	29 to 20	None	None	26	20 to 12
	57	0.3, 0.5	14 to 8	None	None		
G. P. I.	36	0.3, 0.4	80 to 80	None	None	20	86 to 63
T. D.	46	0.4, 0.4	44 to 48	None	None	18	48 to 5
	48	0.3, 0.4	37 to 36	None	None	16	36 to 16
	44	0.3, 0.5	33 to 30	None	None	18	30 to 21
	51	0.3, 0.3	32 to 20	None	None	18	20 to 9
C. S.	65	0.3, 0.4	31 to 36	None	None	12	36 to 29
M.	70	0.2, 0.3	234 to 284	None	None	20	284 to 50
C. S.	58	0.4	100 to 100	None	None	18	100 to 19
M.	59	0.3	85 to 125	None	None	18	125 to 20
M.	42	0.2	9,800 to 9,800	None	None	15	9,800 to 7,300

* In this and in the following tables T. D. = tabes dorsalis; C. S. = cerebrospinal syphilis; M. = syphilitic meningitis; G. P. I. = general paresis of the insane. The number represents the name of the case, each case appears by its own number throughout the paper.
Everywhere in the paper a single + means complete fixation and is an abbreviation for ++++.

little differential diagnostic importance. Treatment in all cases with high cell counts was followed by more rapid improvement in the symptoms and in the Wassermann reaction and a more rapid fall in the number of cells than in the cases with the low cell counts; from this we may infer that high cell counts represent early involvement of the tissues.

The foregoing inference seems to be evidenced by the fact that too frequent or too large doses of salvarsanized serum are immediately followed by an increase in the spinal fluid cell count, probably a result of irritation. In our experience the cell count in untreated cases has not varied, with the exception that in an occasional tabetic during a severe crisis of pain the cell count temporarily increased. To summarize, the effects of treatment on the intensity of the Wassermann reaction carried the greatest weight, and much reliance was placed on the spinal fluid cell count and considerable importance was put on a progressive, permanent improvement in major symptoms, such as severe pain, ataxia, incoordination, incontinence and abnormal mentality.

Other tests were applied to the spinal fluid at irregular intervals. These consisted of the trichloracetic acid test for albumin, the magnesium sulphate and the Noguchi tests for globulin and the reduction test with Fehling's solution. The colloidal gold reaction was tried for a period of three months, but in our experience gave no added information, so it was discontinued.

The protocol given in Table 1 shows the effect of a few doses of intravenous salvarsan on the patients' symptoms and on the spinal fluid, as demonstrable by the Wassermann reaction and the cell count. Those patients who were later given intraspinal salvarsanized serum are also indicated and the effect of the first intraspinal treatment on the cell count is shown; the effect of this one treatment on the Wassermann reaction and on the symptoms will be mentioned in the discussion of the protocol.

The protocol given in Table 1 shows six cases in each of which the patient received six large doses of intravenous salvarsan. One patient, Case 52, was greatly improved in every way; the spinal fluid cell count decreased from 98 to 27, the spinal fluid Wassermann reaction was changed from 0.3 c.c.[2] positive to 1 c.c. negative and the symptomatic improvement, which was marked, is noted in the case report. Another patient, Case 71, evidenced a marked improvement in the spinal fluid Wassermann reaction, from 0.8 c.c. positive to 1.5 c.c. negative, and a drop in the cell count. This was an early case in which the patient had a rash and no other symptoms.

2. These figures throughout refer to the amount of spinal fluid used in the Wassermann test.

The other four patients evinced little or no improvement. In Case 1 the cell count dropped from 44 to 35 during the salvarsan treatments, but one week following the first intraspinal treatment with salvarsanized serum there was a more marked drop in the cell count, that is, from 35 to 7. In Case 22 there was slight temporary improvement in the symptoms only; the first intraspinal treatment produced a provocative reaction in the spinal fluid, and 1 c.c. was required before the intraspinal treatment gave complete fixation, whereas a week after the intraspinal treatment complete fixation was obtained from 0.5 c.c. The patient in Case 3 was somewhat relieved of pain, and ataxia was slightly improved; but the patient in Case 2 showed no demonstrable improvement whatever.

Therefore, of the six patients who each received six large intravenous doses of salvarsan, two evidenced marked improvement and four showed little or no improvement; two of these latter were given intraspinal salvarsanized serum with marked benefit (see Cases 22 and 1 in the case reports). The two markedly improved patients had very recent infections.

To each of five patients were given five large doses of intravenous salvarsan, and all but one showed slight improvement in one way or another. The patient in Case 6 showed a slight improvement in the spinal fluid, and the one in Case 63 showed a drop in the cell count and relief of pain and headache and some improvement in spasticity. The patient in Case 72 showed no improvement whatever, while the one in Case 7 was relieved of headache and dizziness. Patient 67 showed slight improvement in incontinence, and the cell count dropped from 15 to 7. Therefore in these five patients to each of whom was given five doses of salvarsan there was a slight improvement as indicated by the Wassermann reaction in one, improvement as shown in the cell count and in the symptoms in two, marked symptomatic improvement in a third, and no improvement at all in the fifth.

One of the two patients who received four doses of salvarsan each was much improved. This was a patient, Case 37, with syphilitic meningitis, whose primary infection occurred only nine months previous to this treatment. In this case all symptoms were relieved, the spinal fluid cell count dropped from 940 to 33, and the spinal fluid Wassermann reaction changed from 0.5 c.c. positive to 1 c.c. positive. The other patient of this group was not benefited in any way. Thus it is seen that in an early case much improvement may follow only four intravenous doses of salvarsan.

Twelve patients are represented as having received three doses of intravenous salvarsan; one patient, however, Case 52, is included in the first group of patients who received six doses and is repeated here in order to illustrate the improvement which followed only three doses

of salvarsan. This patient showed much improvement symptomatically and in the spinal fluid by a drop in the cell count from 98 to 60. Of the other eleven patients, only one, Case 61, showed any improvement in the Wassermann reaction; namely, a positive reaction with 0.3 c.c. became a positive with 0.4 c.c. Three patients showed a decrease in the cell count, Case 28 from 100 cells to 80, Case 47 from 80 cells to 21, and Case 69 from 17 cells to 10. Three other patients showed slight improvement in symptoms. In two patients the cell count increased. Eight patients who showed no improvement in any way from salvarsan alone were later given intraspinal salvarsanized serum, and the result of the first intraspinal treatment on the cell count is shown; namely, a big drop in every case; and in one patient, Case 45, a provocative Wassermann reaction was obtained in the spinal fluid. Case 23 should be especially noted as it was one of very severe syphilitic meningitis, with all its classical signs and symptoms, and the patient was unimproved by salvarsan and mercury, but great improvement both in the symptoms and in the cell count followed one intraspinal treatment (see case report). Therefore, much improvement may result from three doses of salvarsan, as shown by the patient in Case 52, and some improvement is shown in three others, 23, 49 and 61. The eight patients showing no improvement whatever following three doses of salvarsan, however, did show a marked drop in the cell count following one intraspinal treatment, and four of the eight showed some improvement in the symptoms; in one patient, Case 23, the symptoms were relieved, and in one a provocative reaction was obtained in the spinal fluid.

The remaining twenty cases in this protocol may be considered together, since seventeen patients received two doses of salvarsan and three only one dose. Naturally, little or no improvement in the symptoms or in the Wassermann reaction would be expected from so little treatment, and only a slight change would likewise be expected in the cell count. Nevertheless, the same should hold true for one intraspinal treatment. As a matter of fact, the cell count was reduced slightly in three cases, increased slightly in three and increased markedly in two others, following salvarsan. However, following the first intraspinal treatment, the cell count was reduced in all cases and in seven of these it was greatly reduced and in eleven of the cases it was reduced one half or more. Therefore, in this group of cases one can compare the effect of one or two doses of salvarsan with one intraspinal treatment, and in so doing one finds that the one intraspinal treatment caused a much greater reduction in the cell count than was caused by the salvarsan alone; this fact is conspicuously illustrated in Cases 42, 59, 58 and 70.

Summary of Protocol in Table 1: It seems fair to state that 3, 4, 5 or 6 injections of salvarsan at weekly intervals, occasionally produced great benefit in patients with central nervous system syphilis, such benefit being evidenced by improvement in the patients' symptoms, by the cells count and by the Wassermann reaction in the spinal fluid. Analysis of these three cases in which the patient showed great improvement reveals that they were recent infections, two of the patients having had their primary lesions less than a year previous to the nervous system involvement and the other her primary lesion five years' previously. It is further noted that maximum improvement was obtained by three and four injections of salvarsan in patients with recent infection. Offsetting these two early cases were two other very similar cases, both recent infections, in which the patients derived no improvement from three injections of salvarsan, together with intramuscular mercury, but these same patients did improve greatly in symptoms and there was a large reduction in the cell count following one intraspinal treatment. The other cases in the protocol were all of long-standing infections, so that they cannot be fairly compared with these recent cases, but these old cases do illustrate how slight the improvement may be following five or six injections of salvarsan. Furthermore, some of these patients with long-standing infections who did not improve under salvarsan showed a big drop in the cell count following the first intraspinal treatment. This drop was probably not a belated result from the salvarsan, since three patients who were given only one injection of salvarsan without improvement did show a big drop in the cell count a few days after one intraspinal treatment. Therefore, in all fairness it must be admitted that the protocol shows that some patients with long-standing nervous system syphilis improve remarkably following from three to six injections of salvarsan, whereas others do not improve; that long standing infections are very resistant to salvarsan alone; that patients with early and those with late infections who do not improve under from three to six injections of salvarsan do undergo a considerable improvement as shown by the cell count and some improvement in the symptoms following one intraspinal treatment; so that intraspinal salvarsanized serum in conjunction with intravenous salvarsan would seem to yield better results in all cases than intravenous salvarsan alone.

In the protocol given in Table 2 appear all cases of patients who were given three or four doses of both intravenous salvarsan and intraspinal salvarsanized serum, and for comparison with the previous protocol only the first three or four treatments are tabulated.

In the protocol in Table 2 are shown in fifteen cases only the first three injections of salvarsan, each followed by intraspinal salvarsanized serum, and in fifteen cases are shown the first four double treat-

ments. The amount of salvarsan and the amount of serum injected are presented, together with the spinal fluid cell count before and after each treatment, the change in the Wassermann reaction in the spinal fluid, and the change in the patients' symptoms after the third or fourth treatment, as the case may be.

In the last column much improvement is shown in all patients. All patients with headache, dizziness, vomiting, paresthesia, etc., were relieved of these; all twelve patients suffering pain, were relieved except one, and that one was improved; all seven patients with ataxia were improved, and one was relieved; the five patients with mental disturbances were all improved; incontinence was relieved and objective symptoms were improved by three or four combined treatments.

Improvement was shown by the Wassermann reaction in the spinal fluid in all but four of the twenty-nine cases. Although this improvement amounted to but 0.1 c.c. less positive, much change following so little treatment could not be expected.

The table shows in most cases a gradual drop in cell count following each treatment, and in all but three cases the cell count reached ten or less, and in thirteen cases a normal count was obtained, if we accept five cells as the upper limit of normal. The first treatment was followed by a slight rise in the cell count in one case, and by no change in two cases, but following the second treatment a big drop was obtained in all of these. Reference to the previous protocol, Table 1, shows that eight cases appear there in which the patients obtained no improvement from three to six injections of salvarsan. These same cases appear also in the protocol of Table 2, showing the patients to have improved in every way following three or four combined treatments. Likewise, in Table 1, several patients who showed no improvement following three injections of salvarsan present a record in Table 2 of improvement following three or four combined treatments.

Summary of Protocol in Table 2: It is evident that three or four injections of salvarsan and salvarsanized serum together were followed by much improvement in all patients; that pain, headache, dizziness, vomiting, paresthesia, etc., were relieved, that ataxia and mental disturbances became less severe, and that no patient became worse. There was a slight diminishing of the intesity of the positiveness of the Wassermann reaction in all but five cases. The cell count in all cases showed a marked decrease, in thirteen cases it was reduced to a normal of five and in only three cases did it not approach ten. The one patient, Case 15, who showed the least symptomatic improvement, evinced no change in the Wassermann reaction, and the cell count reached only 31. A comparison of this table with the preceding one shows better results in every way followed the combination treatment

TABLE 2.—Effect of Three or Four Doses of Intravenous Salvarsan and Intraspinal Salvarsanized Serum on the Cell Count, the Wassermann and the Clinical Symptoms

Case Number		Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Change in Wassermann Reaction, C.c.	Clinical Improvement
T. D.	39	128	0.3	20	38	0.4	18	25	0.4	20	19	0.4	20	6	0.5+ to 0.8+	Pain and ataxia less
G. P. I.	21	166	0.3	20	11	0.4	20	16	0.4	20	..	...	..	..	0.05+ to 0.1+	Headache, paresthesia relieved
	11	145	0.3	14	90	0.4	22	30	0.5	18	10	0.4	20	6	0.05+ to 0.2+	Headache, aphasia, diplopia relieved
T. D.	15	108	0.4	16	..	0.4	18	..	0.5	20	31	...	..	..	None	Incontinence, ataxia less
	17	90	0.4	14	47	0.5	20	13	0.5	20	15	0.5	22	5	0.2+ to 0.3+	Pain relieved, ataxia less
C. S.	18	84	0.4	20	40	0.4	20	16	0.4	23	10	0.4	26	10	0.2+ to 0.3+	Mentality improved
G. P. I.	36	86	0.4	20	63	0.5	20	40	0.6	20	30	0.6	22	32	0.2+ to 0.3+	Pain relieved, mentality improved
T. D.	29	87	0.3	18	86	0.6	18	15	0.4	25	11	...	..	..	0.1+ to 0.2+	Ataxia, paresthesia relieved
	1	35	0.4	18	7	0.5	20	2	0.6	16	1	0.6	20	1	None	Incontinence relieved, ataxia less
	6	32	0.3	20	30	0.4	20	20	0.5	18	10	...	..	..	0.2+ to 0.3+	Pain, paresthesia relieved
C. S.	45	14	0.6	16	5	0.6	18	4	0.5	25	..	...	..	..	1.0+ to 1.0—	Paresthesia relieved, mentality improved
T. D.	48	37	0.2	18	16	0.4	20	25	0.6	18	8	0.6	20	1	0.2+ to 0.5+	All symptoms relieved
	44	33	0.5	20	21	0.5	22	30	0.4	20	20	0.5	20	..	None	Symptoms relieved, ataxia less
	41	45	0.3	20	17	0.6	25	..	0.6	26	7	...	18	1	0.3+ to 0.6+	Tremor relieved, mentality improved
	43	40	0.3	18	33	0.4	22	15	0.4	26	10	0.4	22	1	0.1+ to 0.2+	Gastric symptoms relieved
G. P. I.	13	43	0.5	20	13	0.6	20	10	0.6	.	5	...	..	..	0.05+ to 0.2+	Pain, headache, dizziness relieved
	20	57	0.6	18	16	0.5	20	16	0.5	22	7	...	..	..	0.3+ to 0.4+	Pain, vomiting relieved
C. S.	10	47	0.6	16	55	0.6	18	28	0.5	20	16	0.5	20	5	0.2+ to 0.4+	Ataxia relieved, mentality improved
T. D.	14	35	0.4	20	26	0.5	20	20	0.5	20	16	0.5	25	5	0.1+ to 0.2+	Pain, vomiting relieved
	19	18	0.4	16	9	0.5	18	5	0.4	20	5	0.4	18	3	None	Pain, dizziness, depression relieved
C. S.	8	63	0.4	18	34	0.5	20	9	0.6	18	5	...	..	..	0.3+ to 0.4+	Headache, dizziness relieved
T. D.	9	25	0.4	20	20	0.5	22	8	0.5	20	7	...	..	..	0.3+ to 0.4+	Pain, paresthesia relieved
	5	26	0.4	20	9	0.6	20	10	0.6	18	9	...	..	..	0.2+ to 0.3+	Pain, paresthesa relieved
	16	16	0.3	18	10	0.5	20	3	0.4	16	3	...	..	..	None	Pain, paresthesia, dizziness relieved
C. S	65	36	0.3	20	29	0.5	25	6	0.6	20	4	0.6	23	..	0.1+ to 0.8+	Diplopia relieved, mentality improved
T D.	47	21	0.3	20	7	0.4	25	3	0.4	26	1	0.4	20	3	0.2+ to 0.3+	Pain relieved
	40	18	0.3	18	11	0.5	20	16	0.4	28	15	0.4	20	6	0.2+ to 0.5+	Ataxia relieved
	64	64	0.4	23	30	0.4	20	9	..	20	..	...	..	..	0.5+ to 0.6+	Pain relieved
	51	39	...	16	32	0.3	21	20	0.4	22	9	...	..	..	0.4+ to 0.6+	Pain relieved
	74	16	0.6	18	5	0.6	15	2	...	..	..	...	..	..	0.2+ to 0.4+	

of intravenous salvarsan and intraspinal salvarsanized serum than followed salvarsan alone.

We now desired to determine the effect of intraspinal salvarsanized serum alone. For this method of treatment we selected cases with a negative Wassermann reaction in the blood serum, but with positive findings in the spinal fluid. The results appear in the protocol given in Table 3.

The protocol in Table 3 consists of twenty cases in which the patients were treated with intraspinal salvarsanized serum alone. For comparison with the preceding protocol only the first three or four intraspinal treatments and their results are tabulated. The Table shows the amount in cubic centimeters of salvarsanized serum given at each treatment, the cell count before and after each treatment, the resultant change in the Wassermann reaction, and the improvement in symptoms The last two cases, 60 and 62, should be excluded when comparing this protocol with the former one, since both patients were given two intraspinal treatments with normal serum and one intraspinal treatment with salvarsanized serum.

The improvement in symptoms following three or four intraspinal treatments with salvarsanized serum was marked in all cases; those patients complaining of pain, headache, diplopia, numbness, etc., were relieved; those with ataxia were improved; and the three with signs and symptoms of meningitis were relieved.

The Wassermann reaction in three cases showed no change after three treatments and in two others it was negative before treatment. In thirteen cases the positiveness of the Wassermann reaction was diminished, this amounting to 0.1 c.c. in eight cases, to 0.2 c.c. or more in five others and in one case the reaction which was positive with 0.5 c.c. before treatment became negative with 1 c.c. after three treatments. (Compare this latter case with the patient in Case 52, in whom the same result was accomplished by three doses of intravenous salvarsan.) The ten cases starred ultimately became negative with 2 c.c. after more treatment.

The spinal fluid cell count diminished in all cases but one, and this one had only seven cells before treatment. In most cases the cell count diminished gradually, but the three cases with the high counts showed a rapid reduction. Eight cases had a normal cell count after three treatments, and in five others it had diminished to twelve or less. Case 27 illustrates the effect on the cell count of too frequent treatments, as following each of the first two treatments the cell count was diminished, but following the third treatment the count was increased by over 100 cells; however, the cells reached the previous low level after treatment was omitted for two weeks. Accompanying the increased cell count due to overtreatment in this latter case was a

TABLE 3.—Effect of Three or Four Doses of Intraspinal Salvarsanized Serum Alone on Cell Count, Wassermann Reaction and Clinical Symptoms

Case Number		Cell Count	Salvarsanized Serum, C.c. Gm.	Cell Count	Salvarsanized Serum, C.c. Gm.	Cell Count	Salvarsanized Serum, C.c. Gm.	Cell Count	Change in Wassermann Reaction, C.c.	Clinical Improvement
T. D.	26	40	15 of 0.6	30	25 of 0.6	14	27 of 0.5	5	None*	Pains relieved
	27	210	14 of 0.4	100	27 of 0.5	37	20 of 0.4	165	0.4+ to 0.5+*	Pains relieved, ataxia less
	34	52	16 of 0.4	26	20 of 0.4	30	18 of 0.4	5	0.1+ to 0.2+	Pain, dizziness relieved, ataxia less
	25	30	15 of 0.4	3	30 of 0.4	2	25 of 0.6	0	None	Pain, dizziness, numbness relieved
	4	15	20 of 0.4	10	20 of 0.4	9	20 of 0.4	4	0.4+ to 0.5+*	Pain, headache, insomnia relieved
	38	103	20 of 0.4	48	20 of 0.4	40	18 of 0.6	27	0.2+ to 0.3+*	Pain relieved
	22	7	20 of 0.4	6	15 of 0.6	6	20 of 0.6	6	0.5+ to 0.6+	Pain relieved, ataxia less
	24	7	14 of 0.4	5	30 of 0.4	3	21 of 0.4	3	0.4+ to 0.6+*	Gastric crises relieved temporarily
	33	5	15 of 0.4	3	20 of 0.4	3	20 of 0.4	1	0.6+ to 0.9+*	Pain, numbness relieved
	32	60	20 of 0.4	23	18 of 0.5	11	20 of 0.5	..	1.0—	Pain, headache relieved
	31	27	15 of 0.4	13	20 of 0.6	7	25 of 0.5	..	1.0—	Pain relieved, ataxia less
C. S.	12	43	15 of 0.4	20	20 of 0.5	9	20 of 0.5	..	0.3+ to 0.4+	Headache relieved
	35	150	20 of 0.5	75	20 of 0.5	20	20 of 0.5	12	None	Headache, diplopia relieved
M.	23	533	20 of 0.4	272	20 of 0.5	100	25 of 0.6	46	0.1+ to 0.2+*	Headache, diplopia, positive Kernig's, stiff neck relieved
	42	9,800	15 of 0.4	7,300	15 of 0.4	2,500	20 of 0.6	125	0.05 to 0.2+*	Opisthotonos, positive Kernig's, stiff neck relieved
T. D.	64	30	16 of 0.6	9	20 of 0.6	15	25 of 0.6	3	0.5 to 0.8+	Pain relieved, incontinence less
	66	29	15 of 0.4	16	15 of 0.6	12	20 of 0.6	10	None	Pain relieved
	50	16	16 of 0.5	11	20 of 0.5	11	20 of 0.5	5	0.6+ to 0.7+	Pain relieved
G. P. I.	60	93	20 normal	97	20 normal	94	15 of 0.4	53	None	
?	62	7	20 normal	8	20 normal	10	20 of 0.4	123	1.0—	Severe pain for four days

* These cases ultimately gave a negative Wassermann reaction in the spinal fluid with 1 or 2 cubic centimeters following more treatment.

slight remission in the symptomatic progress, and the spinal fluid showed the presence of red blood cells; these same findings resulted a second time in this same case and also occurred in two other cases following a larger number of treatments. In Case 60, which was one of general paresis of the insane with a positive blood reaction, the patient was given two intraspinal treatments with normal syphilitic serum without producing any effect on the cell count; but following one intraspinal treatment with salvarsanized serum the cell count diminished one half. In Case 62, which was not a case of syphilis and had negative reactions in both blood and spinal fluid and a cell count of eight, the patient was given two intraspinal treatments with syphilitic serum without producing any effect on the cell count; however, following one intraspinal treatment with salvarsanized serum, the cell count increased to 123, many red blood cells were present, and the patient complained of severe pain for four days. These two latter cases serve as controls, in that syphilitic serum, not salvarsanized, had no effect on the cell count, whereas salvarsanized syphilitic serum produced beneficial effects, shown by a big drop in the cell count in the case of the syphilitic; but in the case of the nonsyphilitic the salvarsanized syphilitic serum produced ill effects, evidenced by a greatly increased cell count, the presence of red blood cells in the spinal fluid and severe pain. Therefore, one must admit that there is something present in salvarsanized serum that is absent in syphilitic serum, and this something produced beneficial effects in the case of the syphilitic, and ill effects in the case of the nonsyphilitic.

In summarizing this protocol we think it shows the advantage and value of intraspinal salvarsanized serum alone, and that it is further proof that intraspinal salvarsanized serum is a great adjunct to intravenous salvarsan. In certain cases in which intravenous salvarsan is contraindicated intraspinal salvarsanized serum may be given with safety and with possible success; the patient in Case 64, who had edema, and albumen and casts in the urine following intravenous salvarsan, was later given intraspinal salvarsanized serum alone and rapid improvement followed.

So far in this paper we have attempted to show the results following a limited number of treatments which were given by the three different methods. By so doing we have attempted to bring out the value of each method, and to show that when satisfactory results do not follow one method, for instance salvarsan alone, another method, the combination of salvarsan with intraspinal salvarsanized serum, may yield rapid results, thus rendering the treatment of central nervous system syphilis less discouraging. The remainder of the paper is concerned with the entire treatment and its results in each case, and with the condition of the patient after an interval without any treatment.

The patients treated with salvarsan alone are quite thoroughly discussed in connection with the protocol given in Table 1, so that only a few words are necessary before dismissing this method of treatment. Cases M. 37, C. S. 63, C. S. 71 and C. S. 52 were distinctly benefited by salvarsan alone. In Case M. 37, one of meningitis following the primary lesion by only nine months, the patient, whose serum reaction was positive and whose spinal fluid contained 940 cells and was positive with 0.5 c.c., was relieved of all symptoms and signs of meningitis, and the spinal fluid cell count was reduced to 33 and the Wassermann reaction to 1 c.c. positive by four doses of salvarsan. Case C. S. 52 is the record of another patient with very recent infection who was greatly improved by six doses of salvarsan; the spinal fluid cell count dropped from 90 to 20, and the Wassermann reaction was changed from 0.3 c.c. positive to 1 c.c. negative. The record in Case C. S. 71 is that of a patient whose only symptom was a late rash, which was preceded by a primary lesion by less than four years. He was given six injections of salvarsan, following which the spinal fluid cell count became normal and Wassermann reaction became negative with 1.5 c.c. In Case C. S. 63 the patient complained of pain, headache and spasticity of the legs. He had had a primary lesion four years before. Following five doses of salvarsan there was no change in the spinal fluid Wassermann reaction, although the cell count became normal and the pain and headache were relieved. Three more doses of salvarsan, a total of eight, changed the Wassermann reaction in the spinal fluid from 0.1 c.c. to 0.3 c.c. positive; and four more injections, a total of twelve, changed it from 0.3 c.c. positive to 0.4 c.c. positive. Therefore, in these four patients, all with recent infections, satisfactory results followed salvarsan alone.

Nine other patients, all with much older infections than the above four, were treated with as many or more injections of salvarsan than were the above four patients, and little or no benefit resulted. The patients with the records given in Cases T. D. 1, 2, 4, and 22 were given respectively six, six, nine, and twelve injections of salvarsan without any benefit in the symptoms or in the laboratory findings; however, in all of these cases satisfactory results followed when intraspinal salvarsanized serum was used either alone or in conjunction with intravenous salvarsan. The patients in Cases T. D. 3, 6, and 67 were somewhat improved symptomatically following six intravenous doses of salvarsan, although there was practically no change in the laboratory findings. In case 7 the patient was relieved of symptoms following five doses of salvarsan, but no improvement was noted in the laboratory findings. Case C. S. 72 is the record of a patient who derived no benefit in any way from five doses of salvarsan, but when intraspinal salvarsanized serum was given in conjunction with intra-

venous salvarsan, the spinal fluid cell count quickly fell, the Wassermann reaction became more faintly positive, and there was an improvement in the patient's sensory symptoms.

The following summary seems justifiable from this series of thirteen cases in which the patients were treated with salvarsan alone. Patients with recent cases of syphilitic meningitis and cerebrospinal syphilis may be greatly benefited or even relieved by salvarsan alone. Those with older infections, such as tabes dorsalis and cerebrospinal syphilis, derive little or no benefit from salvarsan alone as a rule; however, an occasional case may be benefited or relieved symptomatically only.

The protocol outlined in Table 4 gives diagrammatically a fair idea of the treatment and the results obtained in the patients treated with intravenous salvarsan or diarsenol,[1] and with intraspinal salvarsanized or diarsenolized serum. The patients in the thirty cases comprising the protocol received a total of 215 intravenous and 188 intraspinal treatments. Ten other patients belong to this group, but their cases are not shown, as each was given, for various reasons, only two double treatments; most of these cases appear in other parts of this paper. In twenty-one cases the diagnosis was tabes dorsalis, in three it was cerebrospinal syphilis, and in six it was general paresis of the insane. The results of treatment will be considered as immediate and final. By immediate results is meant symptomatic improvement, and a decrease in the positiveness of the Wassermann reaction and a decrease in the spinal fluid cell count. By final results is meant whether improvement was only temporary or permanent and whether the patient, who was previously incapacitated, was benefited enough to be able to resume work, or in other words, was there any economic value derived from treatment.

As an immediate result from treatment, pain, the most frequent symptom, which was present in nineteen cases, was relieved, as was also headache, dizziness, paresthesia, anesthesia, vomiting, indigestion, diplopia and incontinence. Those patients with such mental symptoms as irritableness, aphasia, impaired memory and depression were all improved, and in many these symptoms were so subdued as to be rendered unnoticeable. Ataxia, which was present in eighteen cases, was relieved in eight, markedly reduced in five and much reduced in five. The only physical sign that was changed was that in only one case a positive Romberg became negative.

The Wassermann reaction in the spinal fluid was diminished in intensity in twenty-five of the thirty cases. In eight of these the improvement was only 0.1 c.c., in ten it was from 0.3 c.c. to 0.5 c.c. diminished, and in five there was a greater improvement, the reaction becoming negative with 1 c.c. The amount of treatment cannot be

TABLE 4.—Effect of Intravenous Salvarsan with Intraspinal Salvarsanized Serum

Case Number		Number of Treatments: Intravenous Salvar.	Number of Treatments: Intraspinal Serum	Change in Wassermann Reaction, C.c.	Clinical Improvement	Interval Without Treatment, Months	Remarks
T. D.	5	4	4	0.2+ to 0.3+	Pain, diplopia relieved; ataxia less	27	No return of symptoms
C. S.	1	28	24	0.2+ to 0.6+	Pain, incontinence relieved; ataxia relieved tempor.	20	Relapse in ataxia
T. D.	6	8	5	0.2+ to 1.0—	Pain, ataxia, incontinence, paresthesia relieved	8	No return of symptoms
	9	4	4	0.2+ to 0.3+	Pain, paresthesia relieved	24	No return of symptoms
	15	4	3	None	Pain, incontinence relieved; ataxia less	19	No return of symptoms; ataxia less
	16	3	3	None	Pain, ataxia relieved; Romberg became negative	24	No return of symptoms
	17	7	6	0.2+ to 0.4+	Pain, incoordination, anesthesia relieved	12	No return of symptoms; is working†
C. S.	8	3	3	0.3+ to 0.4+	Headache, dizziness relieved; memory improved	25	No return of symptoms; is working
G. P. I.	10	7	5	0.2+ to 0.5+	Ataxia relieved, aphasia less, memory improved	14	No return of symptoms; is working
	11	9	9	0.05+ to 0.4+	Ataxia, headache, diplopia relieved; memory improv.	18	No return of symptoms; is working
	21	3	3	0.05+ to 0.1+	Headache, paresthesia relieved; memory improved	4	Died of cerebral hemorrhage
T. D.	14	9	10	0.1+ to 0.4+	Pain, ataxia relieved	10	No return of symptoms; is working
	46	7	4	0.4+ to 0.9+	Pain, diplopia relieved	6	No return of symptoms; is working
	44	5	4	None	Headache, vomiting, ataxia relieved	6	No return of symptoms; is working
C. S.	45	8	3	1.0+ to 1.0—	Pain, ataxia relieved; mentality improved	6	No return of symptoms; is working
G. P. I.	36	4	4	None	Pain relieved, mentality improved	9	Mental relapse
	13	17	17	0.05+ to 0.4+	Pain, headache, dizziness, deafness relieved	3	One attack unconsciousness
T. D.	42	6	7	0.1+ to 0.2+	Pain, ataxia, dizziness, indigestion relieved	8	No return of symptoms; is working
	39	6	6	0.5+ to 1.0—	Pain relieved, ataxia greatly lessened	4	No return of symptoms; is working
G. P. I.	18	9	6	0.2+ to 0.4+	Symptoms relieved	3*	Died of pneumonia
T. D.	19	6	5	None	Pain, dizziness, depression, gastric symptoms relev.	4*	Died of pneumonia
	20	7	5	0.3+ to 0.4+	Pain, vomiting relieved	4*	Died of pneumonia
	47	7	3	0.1+ to 0.3+	Pain, indigestion relieved	2	No return of symptoms; is working
	40	9	9	0.3+ to 1.0—	Paresthesia, weakness relieved; ataxia greatly lessened	1	No return of symptoms; is working
	41	7	7	0.3+ to 0.6+	Headache, numbness relieved; ataxia greatly lessened	2	No return of symptoms
	29	13	12	0.1+ to 0.4+	Headache, dizziness, ataxia relieved	7	No return of symptoms; is working
	48	6	5	0.2+ to 0.5+	Pain, paresthesia relieved; ataxia lessened	3	No return of symptoms
	49	4	3	0.4+ to 0.5+	Pain, incontinence relieved; ataxia lessened	4	Because of edema, albumin, casts, salvarsan omitted
	51	2	4	0.4+ to 0.6+	Pain, gastric symptoms, ataxia lessened	3	No return of symptoms
	65	6	5	0.1+ to 2.0—	Dizziness, diplopia, incontinence relieved	1	Weakness of legs

* Weeks. † Previous to treatment this patient was unable to work.

correlated with the change in the Wassermann reaction. In one case twelve treatments changed the reaction from 0.1 c.c. to 0.4 c.c. positive, while in another case nine treatments changed the reaction from 0.3 c.c. positive to 1 c.c. negative. Many other similar comparisons may be drawn from the above protocol. The blood serum Wassermann reaction became negative in only one case.

No mention is made in the protocol of the effect of treatment on the spinal fluid cell count, as this has been mentioned earlier in the paper, where it was shown that four double treatments reduced the cell count to normal in nearly every case. No parallel can be drawn between the improvement in the cell count and in the Wassermann reaction. Symptomatic sensory improvement parallels fairly closely the diminishing of the cell count, as both occur during the early treatments, and after three or four treatments the cell count is usually at or near normal and sensory symptoms are usually relieved.

As a final result from treatment, thirteen patients out of fifteen previously incapacitated were restored in their economic value; they became able to work and did work. Two others who were unable to walk were improved to such an extent as to be able to get around with the aid of a cane. Four patients relapsed: one patient with tabes had a relapse in ataxia while under treatment, two with general paresis of the insane had mental relapses, one relapse being only slight and temporary; one patient with cerebrospinal syphilis had a relapse of weakness probably of cerebral origin. Four patients have died: three of these died of pneumonia one month after treatment, and the fourth, with a blood pressure of 240 mm. of mercury, died four months later of cerebral hemorrhage. The length of time which has elapsed since treatment was stopped has not been long in many cases. Reference to the protocol shows that in four cases a period of two years has elapsed, in three others eighteen months or more, in two others one year or more, and in eight others a period of six months or more has elapsed without untoward symptoms. The best and most permanent results were obtained in the cases of tabes; two of the six patients with general paresis were restored to working capacity and have shown no return of symptoms for fourteen and seventeen months, respectively; two of the three patients with cerebrospinal syphilis have been free from symptoms for six and twenty-five months respectively, one of these having been previously unable to work.

The protocol in Table 5 consists of seventeen cases in which the patients were treated with salvarsanized serum intraspinally and nothing else. Tabes dorsalis was the diagnosis in thirteen cases, syphilitic meningitis in two cases and cerebrospinal syphilis in two cases. The number of treatments which each patient received, the improvement in the symptoms and in the Wassermann reaction in the spinal fluid,

TABLE 5.—Effect of Intraspinal Salvarsanized Serum Alone on the Wassermann Reaction and on Clinical Symptoms

Patient		No. of Intraspinal Serum Treatments	Change in Wassermann Reaction, C.c.	Clinical Improvement	Interval Since Treatment, Months	Remarks
T. D.	4	27	0.4+ to 2.0—	Pain, headache, insomnia, depression relieved	12	No return of symptoms; is working*
C. S.	12	13	0.3+ to 0.7+	Headache, anesthesia relieved; sight slightly improved	24	Occasional headache; is working
M.	23	17	0.1+ to 1.0—	Symptoms and signs of meningitis relieved	4	No return of symptoms; is working
T. D.	24	8	0.4+ to 1.0—	Gastric crises relieved	12	No return of symptoms
	25	10	None	Pain, dizziness, incontinence relieved; ataxia less	8	No return of symptoms; is working
	26	10	0.2+ to 1.0—	Pain relieved, sight improved, ataxia less	13	No return of symptoms; is working
	27	22	0.4+ to 2.0—	Pain, dizziness relieved, ataxia less	6	No return of symptoms; is working
	31	3	1.0—	Pain relieved, sight greatly improved, ataxia much less	14	No return of symptoms
	32	3	1.0—	Pain, headache, insomnia relieved	13	No return of symptoms; is working
	33	7	0.5+ to 1.0—	Pain, numbness relieved; ataxia less	4	No return of symptoms
	34	13	0.1+ to 0.4+	Pain, dizziness relieved; ataxia less	4	No return of symptoms
C. S.	35	5	None	Symptoms relieved	12	No return of symptoms; is working
T. D.	38	8	0.3+ to 1.0—	Pain, vomiting relieved; ataxia less	6	No return of symptoms
M.	42	9	0.05+ to 2.0—	Symptoms and signs of meningitis relieved	9	No return of symptoms; is working
T. D.	64	5	0.5+ to 0.9+	Pain relieved, incontinence less	2	No return of symptoms
	66	4	0.4+ to 0.5+	Pains relieved	2	No return of symptoms
	22	9	0.5+ to 0.9+	Pain, ataxia, numbness relieved	2	Slight relapse in ataxia, improving

* Previous to treatment this patient was unable to work.

the interval since treatment was omitted and the present condition of the patients are all indicated in the protocol. This protocol is almost an exact reproduction of the previous protocol as to temporary and permanent improvement, the differences being that the former illustrated cases with a positive serum reaction and positive spinal fluid findings, in which the patients were treated with salvarsan and salvarsanized serum, whereas, the latter protocol illustrates cases, with only positive spinal fluid findings, in which the patients were treated with only salvarsanized serum; furthermore in the latter group the Wassermann reaction became negative in more cases.

As an immediate result, pain, headache, dizziness, numbness, etc., were relieved; eye-sight was definitely improved in two patients, one of the two patients having incontinence was relieved and one improved. The one patient with gastric crises was practically relieved, whereas salvarsan had given no relief. A very noticeable improvement followed in the seven patients showing ataxia; one patient who showed no improvement following six treatments of salvarsan was relieved by the same number of serum treatments; of the other six ataxia patients four were unable to walk about the house previous to treatment, but these improved rapidly under treatment. The most striking improvement followed in the two patients with meningitis. One, a child, whose spinal fluid showed 9,800 cells and a positive reaction with 0.05 c.c., with stiff neck, opisthotonos and double Kernig, was relieved of signs and symptoms by three intraspinal treatments, and the cell count dropped from 9,800 to 126. The other patient, whose spinal fluid showed 550 cells and a positive reaction with 0.1 c.c., with stiff neck, double Kernig, and internal strabismus, was relieved of the signs and symptoms by two intraspinal treatments, and the cell count dropped from 550 to 100; the latter case had been given intensive antisyphilitic treatment with salvarsan, mercury, and potassium iodid without relief. Both of these cases ultimately gave negative reactions in the spinal fluid and had a normal cell count (see case reports). Three patients reacted too severely to weekly treatments, but this was overcome by two week intervals.

The Wassermann reaction showed no change following treatment in two cases and in two others it was negative before treatment. In one case a provocative reaction was obtained in the spinal fluid following one intraspinal treatment. The spinal fluid became negative with 1 c.c. in eight cases; in three of these 2 c.c. were tested and found to be negative, as was also the globulin test negative. Two cases showed a decrease in the positiveness amounting to 0.3 c.c., two others 0.4 c.c., and one 0.5 c.c. Therefore in this protocol more cases became negative, and in those which did not become negative, a greater change took place than did in the cases of the previous protocol. The cases of two

patients are of particular interest, in that the serum repeatedly gave a negative reaction while they were being treated intraspinally; but about the time the spinal fluid became negative the serum became positive, and much salvarsan was required to make it negative again.

As the spinal fluid cell count has already been referred to, suffice it to mention that the cell count rapidly decreased and paralleled closely the sensory improvement.

Some permanent results might be mentioned. Nine patients previously unable to work were so much improved by treatment that all have been working since treatment was omitted. One patient had a return of headache after eight months and two had a slight relapse in ataxia, not enough, however, to incapacitate them, and the relapse was only temporary and immediately followed treatment. Seven patients have been observed for twelve months or more since treatment was stopped, and there has been no retrogression in any of them; four others have gone six months or more without untoward symptoms.

Since several of these patients showed no improvement following the use of salvarsan, but improved rapidly while being treated with salvarsanized serum intraspinally alone, it would seem that this class of patients require only the latter form of treatment. Furthermore, there must be some value in salvarsanized serum injected intraspinally.

Summary: Seventy-five patients with central nervous system syphilis were treated with 450 intraspinal injections of salvarsanized serum and with 350 intravenous injections of salvarsan. At first only salvarsan was used, and a few patients improved rapidly. However, in many cases little or no improvement followed from three to six injections, so these patients were then given intraspinal salvarsanized serum in conjunction with the salvarsan, and they improved rapidly under the combined treatment (Swift-Ellis method). As the intraspinal treatment seemed to reinforce the salvarsan, we desired to determine what results would follow the intraspinal method alone. For this method we selected patients with a negative Wassermann reaction in the serum and with positive findings in the spinal fluid. The results from this method closely paralleled those from the double method. Therefore, the following rule has been adopted at this hospital: Patients are first treated with intravenous salvarsan. If satisfactory results do not follow three or four such treatments, they are then given intraspinal salvarsanized serum in conjunction with intravenous salvarsan. Those who have a negative reaction in the serum are given only intraspinal salvarsanized serum. The foregoing scheme is the basis of this paper.

The first part of this paper consists of three protocols which are followed in each case by a discussion. The first protocol consists of cases in which the patients were treated with from three to six injections of salvarsan alone; the second protocol is the record of patients

treated with three or four injections of intravenous salvarsan and intraspinal salvarsanized serum together, and the third protocol shows the record of those treated with three or four intraspinal injections of salvarsanized serum alone. The purpose of this part of the paper is to compare the results following a similar number of treatments given by the three different methods. By this comparison we find that the double (Swift-Ellis) method gave more rapid and more satisfactory results than was given by salvarsan alone, and furthermore, that the intraspinal salvarsanized serum alone gave rapid and satisfactory results. These results were evidenced by improvement in the patient's symptoms, by a drop in the cell count and by a decrease in positiveness of the Wassermann reaction in the spinal fluid.

The latter part of the paper deals with the total treatment given to each patient by the three methods. To thirteen patients were given five or more intravenous injections of salvarsan alone. Four of these patients, three with cerebrospinal syphilis and one with syphilitic meningitis, had very recent infections and were relieved of their symptoms. The spinal fluid cell count was reduced to normal in three cases, and the Wassermann reaction became negative with 1 c.c. in three cases. The remaining nine patients had older infections and they showed little or no improvement in their symptoms and no improvement in the spinal fluid findings.

To thirty patients were given three or more double (Swift-Ellis) treatments, and marked improvement followed in each case. Thirteen patients who were previously incapacitated were restored to working capacity; of eighteen with ataxia, eight were relieved, five were markedly improved and five more were much improved. Twenty-five patients showed improvement in the spinal fluid Wassermann reaction; in ten cases this amounted to from 0.3 c.c. to 0.5 c.c., and in five other cases the reaction became negative with 1 c.c. The spinal fluid cell count became five or less in twenty-five cases. In four cases a period of two years has elapsed since treatment without any return of symptoms, in three others a period of eighteen months and in eight others six months or more. Four patients have shown some form of relapse. One with tabes had a relapse in ataxia, two with general paresis of the insane had a temporary relapse in mentality, while one with cerebrospinal syphilis developed a weakness in the legs probably of cerebral origin.

Seventeen patients were treated intraspinally with salvarsanized serum alone, and all were markedly improved or relieved symptomatically. Nine who were previously unable to work were restored to working capacity. Of the seven patients with ataxia, four previously unable to walk at all, became able to work, and in the other three, in whom the ataxia was not so marked, there is great improvement. The

Wassermann reaction in the spinal fluid became negative with 1 c.c. or 2 c.c. in eight cases, and in five others it was improved from 0.3 c.c. to 0.5 c.c. The spinal fluid cell count became normal in nearly every case. In Cases 23 and 42, both syphilitic meningitis, the patients were relieved in every way. Seven patients have been observed twelve months since treatment was stopped, and four others for six months or more, and they show no return of symptoms. One patient with cerebrospinal syphilis had a return of headache after eight months, and two with tabes had a slight relapse in ataxia, which rapidly cleared up immediately following a treatment.

In one patient a provocative Wassermann reaction occurred in the spinal fluid following the administration of salvarsan, and in two cases a provocative reaction occurred in the spinal fluid following intraspinal treatment. Two patients with repeatedly negative reactions in the serum while under intraspinal treatment developed a positive reaction in the serum about the time the spinal fluid reaction became negative with 1 c.c.

Improvement in symptoms following treatment seemed to parallel fairly closely the drop in the cell count, and those patients with high cell count seemed to improve symptomatically more rapidly and the cell count dropped more rapidly than occurred in those cases with low cell count. The only physical sign which was changed in these cases was that a positive Romberg in one case became negative. More benefit seemed to follow moderate after-treatment reactions than when no reaction occurred. Severe reactions are undesirable and may be avoided by less frequent treatments. In this series of cases no fatal or disturbing results followed treatment.

In this series of cases the total number of cells in the spinal fluid did not vary as a rule. In a few cases of tabes, during severe crises of pain, and in cases immediately following too frequent and too large intraspinal injections of salvarsanized serum, the cell count temporarily increased. Since the cell count has become normal, the patients in Cases 1, 4, 6, 11, 13, 14, 26, 33 and 34 have received lumbar puncture repeatedly for over a year, and those in Cases 23, 25, 27 and 42 for over six months and no variation outside of two or three cells was found in a single instance. Many other patients received lumbar puncture at longer intervals since treatment was stopped and no variation in the cell count was found.

CONCLUSIONS

Patients with recent syphilitic meningitis and cerebrospinal syphilis may be relieved symptomatically by intravenous salvarsan; the spinal fluid Wassermann reaction may become negative with 1 c.c. and the cell count may become normal. Patients with long-standing

cerebrospinal syphilis and tabes may be benefited symptomatically following salvarsan, but little or no change occurs in the spinal fluid findings.

Patients with recent and those with late syphilitic meningitis, cerebrospinal syphilis, tabes and general paresis of the insane are markedly improved following the combination of intravenous salvarsan and intraspinal salvarsanized serum (Swift-Ellis method), and those who fail to improve under salvarsan alone do improve both in symptoms and in spinal fluid findings following this double treatment.

That intraspinal salvarsanized serum greatly benefits patients with central nervous system syphilis is shown by the fact that those with negative serum reactions and with positive spinal fluid findings are symptomatically relieved by this treatment. In many patients the spinal fluid Wassermann reaction becomes negative with 1 c.c., the cell count becomes normal and a negative (Noguchi) globulin test is obtained following sufficient treatment with salvarsanized serum intraspinally without other medication.

CASE REPORTS

TREATMENT WITH SALVARSAN AND INTRASPINAL SALVARSANIZED SERUM

CASE 1.—A man, aged 55, was admitted to the hospital April 10, 1913. A diagnosis of cerebrospinal syphilis was made. Seven years before he had had a chancre followed by a rash. He had had a temporary paralysis of his left leg and the left side of his face, with a marked speech defect one year after his original infection. For two years he had had pains in his left leg and marked ataxia and for one year he had had incontinence of urine and feces and loss of sexual power.

Physical examination showed irregular pupils, which reacted poorly to light. His deep reflexes were exaggerated. The patellar reflex was more active on the right than on the left. There was a positive Babinski and ankle clonus on each side. He walked with a spastic gait and there was marked swaying in the Romberg position. There was some incoordination of the movements of his feet and hands. Over his trunk and face there were irregularly distributed areas of anesthesia for touch. There was a left-sided facial paralysis.

The Wassermann reaction in his blood serum was negative. His spinal fluid showed a cell count of 42 per c.mm. and gave a positive Wassermann reaction with 0.2 c.c. of fluid.

He was given fifteen doses of 0.9 gm. neosalvarsan and thirteen doses of 0.4 gm. salvarsan and twenty-four intraspinal treatments with salvarsanized serum. After the first six doses of neosalvarsan there was no improvement. The first four double treatments relieved the incontinence of urine and feces and the pain and ataxia were improved. At the end of this time he was left without any treatment for two months and during this interval he became more ataxic. During the remaining treatments he continued to get more ataxic until he was able to walk only with a cane. The Wassermann reaction in his spinal fluid changed from positive with 0.2 c.c. to positive with 0.6 c.c. The cell count became normal and has remained so.

Treatment was discontinued twenty months ago. During this interval he has been free from all symptoms except ataxia and this seems to be slowly improving.

CASE 5.—A man, aged 45, was admitted to the hospital Aug. 28, 1913. A diagnosis of tabes dorsalis was made. He had a chancre thirty years before and for the previous five years he had had pains and numbness in his legs and a girdle sensation. For the same length of time he had had attacks of dizziness, which often caused him to fall. For seven months he had had incontinence of urine, failing vision, diplopia and paresthesia over his back. Three months before entrance to the hospital he had developed a Charcot knee.

Physical examination showed unequal pupils, which did not react to light. The deep reflexes of the legs were absent. There was incoordination in the movements of his arms and legs. He could not walk or stand alone.

The Wassermann reaction in his blood serum was negative. The spinal fluid gave a positive Wassermann reaction with 0.2 c.c. and showed a cell count of 26 per c.mm. He was given four doses of neosalvarsan and four doses of salvarsanized serum intraspinally. The treatment relieved his pains and paresthesia, and his diplopia disappeared. The cell count in his spinal fluid became normal and the Wassermann reaction changed from positive with 0.2 c.c. to positive with 0.3 c.c. Twenty-seven months have elapsed since the last treatment and there has been no return of symptoms. At the present time he can walk alone without difficulty except when turning quickly.

CASE 6.—A man, aged 43, entered the hospital Feb. 26, 1914. A diagnosis of tabes dorsalis was made. Twenty years before he had had a chancre which was followed by a rash. He had taken mercury by mouth for eight months and potassium iodid for several years. Five years before he had had several bad falls. Shortly afterward he had noticed that he could not walk straight and that his feet had become numb. For three years he had had shooting pains in his legs. During the previous year he had lost his sexual power and had felt weak and tired.

Physical examination showed a positive Romberg test, absent deep reflexes in his legs and Argyll Robertson pupils.

The Wassermann reaction in the blood serum and in the spinal fluid was positive, with a spinal fluid cell count of 32 per c.mm.

He was given eight doses of salvarsan and five intraspinal treatments with salvarsanized serum. This amount of treatment relieved all of his symptoms and he was able to play tennis and golf. The cell count in his spinal fluid became normal and the Wassermann reaction changed from positive with 0.2 c.c. to negative with 1 c.c. After an interval of six months he was given six additional doses of salvarsan, because his blood serum continued to give a positive Wassermann reaction. Another six months have now elapsed without treatment and the patient is feeling perfectly well.

CASE 8.—A man, aged 42, entered the hospital Nov. 20, 1913. A diagnosis of cerebrospinal syphilis was made. He had had a chancre fourteen years before, which had been followed by a rash and sore throat. He had been treated for three years with mercury by mouth and inunction. Two and a half years before he had been given one dose of salvarsan. During the year previous to entrance he had had very severe headaches, dizziness, difficulty in speech, failing memory and a temporary paralysis of his left face and arm. He had been unable to work for the previous six months.

Physical examination showed a poor reaction of his pupils to light, hyperactive reflexes, ataxia of his left arm and poor memory.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 63 per c.mm.

He was given three doses of salvarsan and three doses of salvarsanized serum intraspinally. This amount of treatment relieved his headaches, dizziness and irritability. The spinal fluid cell count was reduced from 63 to 9 per c.mm. The Wassermann reaction in the spinal fluid was changed from positive with 0.3 c.c. to positive with 0.4 c.c. Twenty-five months after the last treatment he was free from symptoms and had gained thirty pounds in weight.

CASE 9.—A woman, aged 45, entered the hospital Dec. 16, 1913. A diagnosis of tabes dorsalis was made. She had had pains in the legs for several years, but during the previous few weeks the pains had become more severe and had involved the arms and body. She had had some mental disturbance, particularly depression, for several weeks.

Physical examination showed Argyll Robertson pupils, hyperactive reflexes and disturbed sensation about the waist.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a cell count in the latter of 25 per c.mm.

She was given four doses of neosalvarsan and four doses of salvarsanized serum intraspinally. At the end of six weeks all pain and hyperesthesia were relieved. Mentally she seemed normal. The spinal fluid cell count was reduced to 2 per c.mm. and the Wassermann reaction was changed so that 0.3 c.c. was required to give a positive test, while at the first observation only 0.2 c.c. was necessary. She was treated last twenty-four months ago and during that time she has had no return of symptoms.

CASE 10.—A man, aged 50, entered the hospital Sept. 23, 1914. A diagnosis of general paresis of the insane was made. The patient had had a chancre twelve years before and had been treated for eighteen months with potassium iodid and mercury by mouth. For a year previous to entrance he had been irritable, restless, inattentive and easily fatigued. Three months previously he had lost his memory for a week and had developed a facial paralysis. Within the previous few weeks he had noticed tremor of his hands, ataxia, periods of mental depression, trouble with his speech and writing.

Physical examination showed Argyll Robertson pupils, exaggerated and unequal knee jerks, tremor of the tongue and facial muscles, poor memory, slurring speech, and handwriting characteristic of general paresis.

The Wassermann reaction was positive in both blood serum and spinal fluid. The spinal fluid cell count was 47 per c.mm.

Seven doses of salvarsan and five intraspinal treatments of salvarsanized serum were given to this patient. At the end of two months there was great improvement in his memory. He was not depressed or irritable. There was no ataxia and he had returned to work. The Wassermann reaction in his spinal fluid was changed from positive with 0.2 c.c. to positive with 0.5 c.c. The cell count was reduced from 47 to 5 per c.mm. The patient was heard from fourteen months after leaving the hospital; at this time he was feeling perfectly well and had no return of his former symptoms.

CASE 11.—A man, aged 62, entered the hospital Feb. 26, 1914. A diagnosis of general paresis of the insane was made. Twelve years before he had had a chancre. For the previous year he had been run down and tired, had had attacks of vomiting and one period of aphasia. He stated that he had given up work because of fatigue, loss of memory, inability to concentrate, diplopia and disturbance in gait.

Physical examination showed that his pupils were unequal and irregular, but reacted to light. All reflexes were hyperactive. There was a positive Romberg test and some tremor of the tongue and muscles of the face. The Wassermann reaction in the blood serum was positive and it was also positive in the spinal fluid with 0.05 c.c. There was a spinal fluid cell count of 145 per c.mm.

He was given nine doses of salvarsan and nine treatments with salvarsanized serum intraspinally. The first few treatments relieved the diplopia, aphasia, abnormal sensations and numbness. Under further treatment his memory gradually improved until it seemed about normal, the tremor of his facial muscles decreased somewhat and he became able to work a full day. The cell count was reduced from 145 to 6 per c.mm. The Wassermann reaction was changed from positive with 0.05 c.c. to positive with 0.4 c.c. Eighteen months have passed since the last treatment and the patient still feels well, his sight

and hearing are normal, his memory is good and he has no ataxia. He has worked every day during this period. The examination of his spinal fluid at the present time shows 6 cells per c.mm. and a positive Wassermann reaction with 0.4 c.c.

CASE 13.—A man, aged 44, entered the hospital Aug. 1, 1914. A diagnosis of general paresis of the insane was made. Six years before he had had a chancre, which was followed by a rash and severe headaches. He had been treated with potassium iodid and inunctions of mercury for about six months. Eight months before he had begun to have headaches, which had increased in severity and frequency. He had become nervous, irritable and unable to sleep. He had become deaf and had suffered from tinnitus. One week before he had become crazed and was unconscious for fifteen hours. Following that attack his headaches had been worse, dizziness had been troublesome and his memory had almost entirely failed.

Physical examination showed a tremor of the face, tongue and hands, characteristic handwriting, unequal and hyperactive reflexes.

The Wassermann reaction in both blood serum and spinal fluid was positive, with a spinal fluid cell count of 43 per c.mm.

He was given fifteen doses of salvarsan and fifteen intraspinal treatments with salvarsanized serum. The first five treatments were at weekly intervals, but later the interval was lengthened to one month. After the first five treatments all headache, dizziness, nervousness and irritability disappeared and he was able to sleep. The spinal fluid cell count was reduced to 5 per c.mm. After seven treatments he returned to work and said that he felt perfectly well. After the whole amount of treatment the Wassermann reaction in the spinal fluid changed from positive with 0.05 c.c. to positive with 0.4 c.c., with a spinal fluid cell count of 2 per c.mm. The blood serum still gave a positive Wassermann reaction. The patient went for three months without treatment, at the end of this time he had another attack of loss of consciousness. As the spinal fluid showed no relapse he was given six doses of salvarsan.

CASE 14.—A man, aged 45, entered the hospital Aug. 5, 1914. A diagnosis of tabes dorsalis was made. Three years before he had begun to have anorexia, gaseous eructations and regurgitation of food about three hours after meals. One year before he had begun to have severe burning pain in the epigastrium one or two hours after meals. He had also had occasional attacks of vomiting, which relieved the pain. His appetite had failed until only liquids were taken. He had been unable to work and had lost thirty pounds in the previous three months.

Physical examination showed unequal and irregular pupils, which reacted very little to light, and exaggerated knee jerks. The guaiac test in his stools was positive. Gastric lavage showed much stasis. There were two liters of fasting contents. The free hydrochloric acid was 34 and total acidity was 60. There was no blood or lactic acid, but there was much starch and yeast and many sarcinae.

Roentgen ray five hours after a meal with bismuth showed two thirds of the meal remaining in the stomach. Fluoroscopic examination showed gastric atony and occasional antiperistaltic waves. After ten hours about one half of the meal remained in the stomach and after twenty-four hours there was still a large residue. The Romberg test was positive. The gait was markedly ataxic. The Wassermann reaction in the blood serum was positive. The spinal fluid gave a positive Wassermann reaction with 0.1 c.c. and showed a cell count of 33 per c.mm. The diagnosis of gastric ulcer was at this time added to the diagnosis of tabes dorsalis.

He was given six doses of 0.5 gm. of salvarsan and five intraspinal treatments with salvarsanized serum at intervals of two weeks. After this at irregular intervals he was given four doses of salvarsan and six doses of salvarsanized serum intraspinally. After two treatments pain and vomiting dis-

appeared and his appetite improved. After five treatments very little stasis could be demonstrated either by tube or by Roentgen ray and he became free from symptoms. His condition of ataxia improved and he returned to work. After an interval of four months without treatment, although he was still free from symptoms, gastric lavage showed much stasis, free hydrochloric acid of 18 and total acidity of 60. After this, four treatments were given at intervals of three weeks. The cell count in the spinal fluid was reduced to 2 per c.mm. and the Wassermann reaction was changed so that 0.4 c.c. was necessary to give a positive test. The patient meanwhile began to lose strength and weight and was operated on two months later and a large retroperitoneal carcinoma involving the fundus of the stomach was found. Therefore the carcinoma was demonstrated four years after the first symptoms and two years after the first severe pain. It is of interest that his symptoms and stasis disappeared under antisyphilitic treatment and this led to the diagnosis of a syphilitic ulcer of the pylorus complicating the tabes. Ten months have elapsed since the last treatment and seven months since gastro-enterostomy was performed and the patient has gained much in strength and weight and works every day.

CASE 15.—A man, aged 62, entered the hospital May 31, 1914. A diagnosis of tabes dorsalis was made. He had had a chancre forty years before. For eighteen years he had had lancinating pains in his legs and for fourteen years increasing difficulty in walking. Recently he had had incontinence of urine and feces and had been able to walk only with two people to assist him.

Physical examination revealed signs diagnostic of advanced tabes dorsalis. The Wassermann reaction was positive in both blood and spinal fluid, with a spinal fluid cell count of 108 per c.mm.

He was given four doses of salvarsan and three treatments with salvarsanized serum intraspinally at weekly intervals. The last treatment was given nineteen months ago. During this time he has had less incontinence of urine and none of feces. He has had no pain and he can walk very well with one cane.

CASE 16.—A man, aged 35, entered the hospital March 23, 1914. A diagnosis of tabes dorsalis was made. Twelve years before he had had a chancre. Eleven days before he had had tingling and numbness in his fingers and toes and pains in his legs. For six days he had had trouble in walking. His gait had been unsteady and he had fallen repeatedly when he had turned or stopped suddenly. He had also had some dizziness, and had had a sense of pressure about his waist for several days.

Physical examination showed unequal and irregular pupils, which reacted to light. The deep reflexes of the arms and legs were absent. There was marked incoordination in all his movements. The Romberg test was positive.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 16.

He was given three doses of salvarsan and three treatments with salvarsanized serum intraspinally. This relieved the pain, numbness and dizziness completely. His ataxia was greatly decreased, and he was able to walk and to turn quickly without any trouble. His Romberg test was negative and coordination was much improved. The cell count in his spinal fluid fell from 16 to 3 per c.mm. Twenty-four months have elapsed since he was last treated and during this interval he has remained completely free from symptoms.

CASE 17.—A man, aged 52, entered the hospital Dec. 9, 1914. A diagnosis of tabes dorsalis was made. Twenty-five years before entrance he had had a chancre. For ten years he had had a tendency to stagger. For eight years he had had lightning pains in his legs and difficulty in starting his urine. For five years he had had difficulty in controlling his feet and had fallen several times. He had recently had some difficulty in controlling his rectal sphincter. He had had complete loss of sexual power for eight months. All his symptoms had been progressive.

Physical examination showed irregular, unequal pupils, which did not react to light, and absent knee jerks, a positive Romberg test and marked incoordination of the movements of both arms and legs.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 90 per c.mm.

He was given seven doses of salvarsan and six intraspinal treatments with salvarsanized serum. His pains were quickly relieved by treatment and gradually his legs and feet became stronger and more easily controlled. He could walk without falling or stumbling and felt greatly improved in every way. The spinal fluid cell count was reduced from 90 to 5 per c.mm. The Wassermann reaction in the spinal fluid was changed from positive with 0.2 c.c. to positive with 0.4 c.c. Twelve months have elapsed since the last treatment and there has been no return of symptoms.

CASE 18.—A man, aged 48, entered the hospital Nov. 17, 1915. A diagnosis of neurosyphilis was made. He had had a chancre several years before. For several months he had felt tired and irritable.

Physical examination was entirely negative, except for a blood pressure of 200 mm. of mercury.

The Wassermann reaction in both blood and spinal fluid was positive, with a spinal fluid cell count of 80 per c.mm.

He was given nine doses of salvarsan and six intraspinal treatments with salvarsanized serum. His tired feeling was relieved and his disposition became more nearly normal. The cell count in his spinal fluid was unaffected by three doses of salvarsan alone, but dropped to normal after three intraspinal treatments in conjunction with the salvarsan. After the last treatment the Wassermann reaction in his spinal fluid was positive with 0.4 c.c., while at entrance it was positive with 0.2 c.c.

Three weeks after the last treatment he developed lobar pneumonia and died.

CASE 19.—A woman, aged 46, entered the hospital Dec. 30, 1914. A diagnosis of tabes dorsalis was made. For five years she had had frequent attacks of severe headache and vomiting, which lasted for two or three days. For three years she had had shooting pains in the legs and for four months had had marked unsteadiness in gait. For three months she had been unable to pass her urine and had had to be catheterized. She recently had been very dizzy, nervous and depressed mentally.

Physical examination showed Argyll Robertson pupils, absent deep reflexes in both legs and a positive Romberg test.

The Wassermann reaction in both blood serum and spinal fluid was positive with a spinal fluid cell count of 12 per c.mm.

She was given six doses of salvarsan and five intraspinal treatments with salvarsanized serum. After the first treatment with salvarsan the spinal fluid cell count was 18 per c.mm., but directly after the first double treatment the cell count fell to 9 per c.mm. After further treatment all pains and dizziness disappeared and the cell count in the spinal fluid became normal. The mental depression disappeared, there was no sphincter disturbance and she felt well in every way.

One month after the last treatment she died of lobar pneumonia.

CASE 20.—A man, aged 33, entered the hospital Jan. 23, 1915. A diagnosis of tabes dorsalis was made. Ten years before he had had a chancre. For four years he had had pains radiating around the waist, indigestion, nausea and vomiting. During the four days previous to entrance he had had uncontrollable vomiting.

Physical examination showed absent deep reflexes in the legs and Argyll Robertson pupils.

The Wassermann reaction was positive in the blood serum. The spinal fluid showed a cell count of 16 per c.mm. and gave a positive Wassermann reaction with 0.2 c.c.

He was given seven doses of salvarsan and five intraspinal treatments with salvarsanized serum. After three doses of salvarsan the vomiting stopped. Further treatment relieved his pain and the spinal fluid cell count became normal. The Wassermann reaction was positive with 0.4 c.c.

One month after the last treatment he died of pneumonia.

Case 21.—A man, aged 48, entered the hospital Oct. 27, 1914. A diagnosis of general paresis of the insane was made. He had had some local sores on his penis twenty-nine years before and again twenty years later. Five months before he had had a severe mental shock, following which he had acted queerly. He had imagined that he was suspected of killing his brother and had become so unbalanced mentally that he had been under restraint temporarily in an institution. For one week he had had numbness and tingling in his left ankle. He had also had severe headaches, failing memory and loss of energy.

Physical examination showed unequal pupils, which did not react to light. There was marked tremor of the face, lips and tongue, with exaggerated reflexes and a positive Romberg sign. The blood pressure was 240 mm. of mercury and the urine showed an abundance of albumin and a variety of casts.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 166 per c.mm.

He was given three doses of salvarsan and three intraspinal treatments with salvarsanized serum. The first treatment reduced the cell count from 166 to 11 per c.mm. After the final treatment the numbness and headache were relieved and he felt so well that he refused to return to the hospital. Four months later, following a cerebral hemorrhage, he became completely paralyzed and died.

Case 29.—A woman, aged 55, entered the hospital Feb. 9, 1915. A diagnosis of tabes dorsalis was made. For four months she had noticed a staggering gait. For six weeks she had been dizzy and nauseated and had vomited frequently. Directly following one of the attacks of vomiting she had noticed numbness of the right side of her face and general weakness. Staggering recently had become much worse, her legs had felt numb and she had been upset mentally.

Physical examination showed unequal and irregular pupils, absent deep reflexes in the arms and hyperactive knee jerks.

The Wassermann reaction was positive in both blood and spinal fluid, with a spinal fluid cell count of 87 per c.mm.

She was given thirteen doses of salvarsan and twelve intraspinal treatments with salvarsanized serum. After the first five treatments there was complete relief of the numbness, weakness, staggering and mental confusion. The cell count in the spinal fluid was reduced to normal. After the tenth treatment she felt perfectly well. The Wassermann reaction in the spinal fluid changed from positive with 0.1 c.c. to positive with 0.4 c.c. Four months elapsed without treatment and there was no return of symptoms. Two more treatments were given recently in order to get specimens of the spinal fluid. This showed no further change.

Case 36.—A man, aged 54, entered the hospital March 11, 1915. A diagnosis of general paresis of the insane was made. He had had a chancre twenty-eight years before and had had treatment for about seven years. He had had vague headaches for fifteen years and for ten years he had had dizziness, ataxia and joint pains. For ten months he had had progressive mental disturbance. He had been unable to sleep because of severe abdominal pain.

Physical examination showed Argyll Robertson pupils, sluggish and unequal deep reflexes in the legs.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 80 per c.mm. The pain, dizziness and vomiting

were relieved by treatment, but as the patient developed delusions all treatment was omitted. Two months after treatment was discontinued he became clear mentally and has continued so for seven months.

CASE 39.—A woman, aged 40, entered the hospital June 2, 1915. A diagnosis of tabes dorsalis was made. For fourteen years she had had shooting pains in the legs and for a year had been markedly ataxic. For the previous eight months she had been unable to walk about the house without a cane and during the last four months she had been bedridden. For six months she had had pains of such severity in her arms and legs that she had taken from 2 to 10 gm. of aspirin daily.

Physical examination showed unequal and irregular pupils, which did not react to light, and absent knee and ankle jerks. She was unable to stand alone.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 128 per c.mm.

She was given six doses of salvarsan and six intraspinal treatments with salvarsanized serum. All pain was relieved by the first two treatments. After the last treatment she was able to walk about the house without assistance. The changes in the spinal fluid were marked. The cell count became normal and the Wassermann reaction was changed from positive with 0.5 c.c. to negative with 1 c.c. After four months without treatment, during which time there was no return of symptoms, the patient was given four doses of salvarsan, because of a positive Wassermann reaction in the blood serum. The blood serum since that time has given a negative Wassermann test.

CASE 40.—A woman, aged 46, entered the hospital May 24, 1915. A diagnosis of tabes dorsalis was made. For six months she had had weakness of the legs, paresthesia and unsteadiness of gait.

Physical examination showed unequal and irregular pupils, absent deep reflexes in the legs and a positive Romberg test. The patient could barely stand alone.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 18 per c.mm.

She was given nine doses of salvarsan and nine intraspinal treatments with salvarsanized serum. The first five treatments reduced the cell count to normal and the Wassermann reaction was changed from positive with 0.2 c.c. to positive with 0.6 c.c. At this time she became able to walk about the house without difficulty. The last four treatments were given at irregular intervals of one and two months. At the last examination the Wassermann reaction in the spinal fluid was negative with 1 c.c. One month has elapsed since the last treatment. At present she is free from symptoms and is steadily improving in her ability to walk.

CASE 41.—A man, aged 40, entered the hospital June 25, 1915. A diagnosis of tabes dorsalis was made. For sixteen months he had been nervous and easily tired. For six months he had had numbness in the legs, loss of sensation in the feet and unsteadiness. He had had some difficulty in speech and severe frontal headaches.

Physical examination showed absent deep reflexes in arms and legs, ataxia in the right arm and leg and a positive Romberg test.

The Wasserman reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 60 per c.mm.

He was given seven doses of salvarsan and seven intraspinal treatments with salvarsanized serum. After three treatments the spinal fluid cell count was reduced to normal, headache disappeared, tremor lessened and nervousness was relieved. The last four treatments were given at monthly intervals. The ataxia has been much relieved by them and the Wassermann reaction has changed from positive with 0.3 c.c. to positive with 0.6 c.c. Two months have elapsed since the last treatment and there has been no return of symptoms.

CASE 43.—A man, aged 51, was admitted to the hospital June 18, 1915. A diagnosis of tabes dorsalis was made. Twenty-eight years before he had had a chancre which was followed by a generalized rash. He had been treated with mercury by mouth until he was salivated. For two years he had had some dizziness and trouble in walking. He had also had marked constipation and attacks of vomiting.

Physical examination showed unequal pupils, which reacted sluggishly to light, unsteady gait, ataxia of arms and a positive Romberg test.

The Wassermann reaction was positive in both blood serum and spinal fluid with a spinal fluid cell count of 41 per c.mm. He was given three doses of salvarsan, and three intraspinal treatments with salvarsanized serum. This relieved his dizziness and staggering and also his constipation and vomiting. During the next three months he gained twenty pounds. During the last three months he has had three doses of salvarsan and three treatments with salvarsanized serum. He is free from all symptoms. The cell count in the spinal fluid is normal. The Wassermann reaction is positive in both blood serum and spinal fluid.

CASE 44.—A man, aged 48, entered the hospital July 14, 1915. A diagnosis of tabes dorsalis was made. Seventeen years before he had had a chancre. Six months before he had begun to have severe headaches, weakness of the legs, retention of urine and progressive difficulty in walking. For one month before he had been unable to get out of bed. He had vomited frequently, had been nervous, irritable and very forgetful.

Physical examination showed absent deep reflexes in both arms and legs, ataxic gait, positive Romberg test and pupils which reacted very poorly to light.

The Wassermann reaction was positive in both blood and spinal fluid with a spinal fluid cell count of 33 per c.mm.

He was given five doses of salvarsan and four intraspinal treatments with salvarsanized serum. His headache, vomiting and irritability were relieved, and from being unable to get out of bed he improved so that he was able to work. His memory was greatly improved. He has had no treatment for six months. During this time he has been free from symptoms and has worked steadily.

CASE 45.—A man, aged 32, entered the hospital May 4, 1915. A diagnosis of cerebrospinal syphilis was made. Four weeks previous to admission he had had several temporary paralyses of his legs and arms and a more permanent paralysis of his face. For the past week he had had a feeling of constriction in his knees and inability to control his feet and legs and frequent crampy pains in his legs.

Physical examination showed that the left pupil was larger than the right. The knee jerks, Achilles, and epigastric reflexes were exaggerated. There was a double ankle clonus present. The Romberg was markedly positive. There was a spastic gait.

The Wassermann reaction in the blood was positive after a provocative reaction; in the spinal fluid it was negative except after salvarsan provocative, when it was positive with 1 c.c. The spinal fluid cell count was 15 per c.mm.

He was given two doses of salvarsan of 0.3 and 0.5 gm., respectively, three doses of 0.5 gm. each of salvarsan and three intraspinal serum treatments of 20 c.c. each; also three doses of salvarsan of 0.5 gm. each.

The 0.3 gm. of salvarsan produced a provocative positive blood Wassermann reaction and the 0.5 gm. produced a provocative positive Wassermann reaction in the spinal fluid in 1 c.c. amounts; however, the cell count and symptoms were not changed. The first double treatment reduced the cell count to 5 and the patient improved. The next two double treatments relieved all the symptoms and the spinal fluid became negative. Following this, three doses of 0.5 gm. each of salvarsan were given. Six months have elapsed and the patient is still free from symptoms.

CASE 46.—A man, aged 49, entered the hospital April 22, 1915. A diagnosis of tabes dorsalis was made. Eighteen years before he had had two primary sores. These were cauterized and he was given mercury by mouth and potassium iodid for three months. For the past two years he had had pins and needles sensation in his legs and arms. For the past year he had had squint and diplopia.

Physical examination showed that the pupils were inactive to light. The left pupil was larger than the right. There was optic atrophy in both pupils. The biceps and ankle reflexes were just obtainable. The knee jerks were active; the left being larger than the right. The plantar reflexes were exaggerated.

The Wasserman reaction was positive in the blood and spinal fluid, with a spinal fluid cell count of 44 per c.mm.

He was given seven doses of 0.4 gm. each of salvarsan and four intraspinal treatments of 25 c.c. each of salvarsanized serum in four months. The Wassermann reaction in the blood became negative; in the spinal fluid it was changed from positive with 0.4 c.c. to positive with 0.9 c.c., and the spinal fluid cell count was reduced from 44 to 3 per c.mm. The patient was relieved from symptoms and felt better than he had for years. He has been six months without treatment and without return of symptoms.

CASE 47.—A woman, aged 42, entered the hospital Aug. 31, 1915. A diagnosis of tabes dorsalis was made. She had had a chancre and rash twenty-one years before. Fourteen years before she had had a nervous breakdown, with shooting pains in her head, black spots before her eye and shaking all over. Since then she has had frequent knifelike pains across her abdomen, indigestion, and contractions of her lips, fingers, face and elbows. She had one spasm of her whole body. For the past sixteen years she has had shooting pains all over her body and varied indefinite symptoms. For the past year in addition she has had twitching of her eyelids, numbness of her fingers, and she has been sensitive to cold weather.

Physical examination showed that her pupils were inactive to light. The biceps, triceps, periosteoradial, right knee jerk and both ankle reflexes were absent. There was incoordination of the right hand and fingers.

The Wassermann reaction in the blood and spinal fluid was positive, with a spinal fluid cell count of 80 per c.mm.

She was given seven doses of salvarsan and four intraspinal treatments with salvarsanized serum. The first two doses of salvarsan reduced the spinal fluid cell count from 80 to 21, but did not change the Wassermann or improve the symptoms. After that, double treatments were given. The first two of these reduced the cell count to 3, and relieved the pain, numbness and indigestion. Following the remaining treatments the patient felt like a new person. The spinal fluid Wassermann reaction changed from positive with 0.1 c.c. to positive with 0.3 c.c. It is now two months since the last treatment.

CASE 48.—A man, aged 43, entered the hospital Sept. 27, 1915. A diagnosis of tabes dorsalis was made. Twelve years before he had had a chancre and loss of hair. For three and one-half years after that he was given iodid of mercury by mouth. One year before he had begun to have sharp shooting pains in his legs, pins-and-needles sensation in his arms and weakness of his knees. Later he began to stagger. Recently he has had urgency of micturition.

Physical examination showed the periosteoradial and epigastric reflexes absent, knee jerks and Achilles reflexes hyperactive, and the Romberg slightly positive.

The Wassermann reaction was positive in both the blood and spinal fluid, with a spinal fluid cell count of 37 per c.mm.

He was given six doses of 0.6 gm. each of salvarsan and five intraspinal treatments with salvarsanized serum in two months. The first two treatments relieved the pains. The other treatments relieved the paresthesia, weakness and urgency of micturition. The ataxia was greatly lessened, being practically

relieved. The spinal fluid cell count was reduced to 1, the Wassermann reaction from positive with 0.2 c.c. to positive with 0.5 c.c. It is now three months since treatment.

CASE 51.—A woman, aged 35, entered the hospital Aug. 6, 1915. A diagnosis of tabes dorsalis was made. Some years before she had had a chancre. Eight years before she had begun to have sharp, shooting pains in her legs. These increased in intensity until she acquired a morphin habit and took 4 grains of morphin daily. For the previous six years she had had nausea and vomiting accompanying frequent attacks of gastric distress. For the previous five years she had had an unsteady gait, unsteadiness when standing and increasing incontinence of urine until at the time of entrance she dribbled constantly. Eight months before her entrance her right knee cap had slipped out of place and the knee had become swollen and she developed a Charcot knee. For the previous four months she had walked a little with a crutch.

Physical examination showed her pupils reacted sluggishly to light. There was ataxia of the left hand. The biceps, triceps, knee jerks, Achilles and plantar reflexes were absent. She was unable to stand alone.

The Wassermann reaction was positive in both the blood and spinal fluid, with a spinal fluid cell count of 39 per c.mm.

She was given two doses of salvarsan and four intraspinal treatments with salvarsanized serum. The first two treatments relieved the pain and gastric distress somewhat. The morphin was reduced to 1 grain per diem. After the last treatment, which was three months ago, she was free from pain and the spinal fluid Wassermann reaction was positive with 0.6 c.c.

CASE 61.—A woman, aged 39, entered the hospital July 20, 1915. A diagnosis of tabes dorsalis was made. For the previous three years she had had pain in the large joints, and attacks of dizziness, nausea, and vomiting of ten days' duration. The attacks appeared every few months. For the past five months she had pain constantly and loss of appetite, strength and weight.

Physical examination showed that the pupils were irregular. All of her arm and leg reflexes were hyperactive.

The Wassermann reaction was positive in both the blood and spinal fluid, with a spinal fluid cell count of 27.

She was given eight doses of salvarsan and three intraspinal treatments with salvarsanized serum. The pains were relieved early, and there have been no attacks of dizziness. Salvarsan alone seemed to be of much benefit in this case.

CASE 64.—A man, aged 48, entered the hospital Oct. 11, 1915. A diagnosis of tabes dorsalis was made. Eleven years before he had begun to have incontinence of urine while asleep. This progressed until for the previous three years he had had to wear a urinal constantly. For the previous two years he had been ataxic and had been unable to see well at night. He had had alternating attacks of diarrhea and constipation. For the previous ten months he had had pain in the large joints and epigastrium, with edema of the ankles at night and dyspnea. Just previous to his entrance his hands and fingers had been numb with loss of sensation and ataxia of the fingers.

Physical examination showed the pupils to be pinpoint and inactive to light. The reflexes of the arms and legs were absent. There was marked ataxia and incoordination of the arms and legs. The gait was ataxic and stamping.

The Wassermann reaction was slightly positive in the blood; in the spinal fluid it was positive with 0.4 c.c. The spinal fluid cell count was 27 per c.mm.

He was given four doses of salvarsan and three intraspinal treatments with salvarsanized serum. Following this the serum became negative and on account of the edema of the ankles and albumin and casts in the urine only intraspinal serum treatments were continued. No change in the symptoms or in the spinal fluid Wassermann reaction followed the double treatments, although the cell count increased from 37 to 64 and fell back to 30, and the serum Wassermann reaction became negative. The first four intraspinal serum treatments alone

reduced the cell count to 3, changed the Wassermann reaction from positive with 0.4 c.c. to positive with 0.8 c.c. and somewhat relieved the incontinence. The pains were nearly relieved.

CASE 65.—A man, aged 46, entered the hospital Nov. 3, 1915. A diagnosis of cerebrospinal syphilis was made. Twelve years before he had had a chancre followed by a rash, sore throat and headache. At this time he was treated by mouth. Six years before a sudden weakness of the right side had developed. This was followed by recovery of the right arm and partial recovery of the right leg. For the previous six years he had had short attacks of dizziness, faintness and diplopia. These attacks were of ten hours' duration. For the previous year he had had some incontinence of feces. For the previous four days he had had much dizziness and diplopia, his speech had been slow and he had been very absent minded.

Physical examination showed the right pupil to be larger than the left. Diplopia was present. There was tremor of the hand, leg and arm. The reflexes on the right side were hyperactive. There was weakness of the right leg, a double ankle clonus and a positive Babinski and Oppenheim on both sides.

The Wassermann reaction was positive in both the blood and spinal fluid, with a spinal fluid cell count of 65 per cmm.

He was given seven doses of 0.6 gm. each of salvarsan and six intraspinal treatments with salvarsanized serum. The early treatments relieved the diplopia and dizziness and the patient became much clearer mentally. He then developed a sudden weakness of both legs and the incontinence which first cleared up again returned, but mentally he remained improved. The Wassermann reaction in the spinal fluid was modified from positive with 0.1 c.c. to negative with 2 c.c. The spinal fluid cell count became normal, but the blood Wassermann reaction remained positive.

TREATMENT WITH SALVARSAN

CASE 2.—A man, aged 59, entered the hospital July 20, 1913. A diagnosis of tabes dorsalis was made. The patient had had a chancre thirty-two years before and for the previous fourteen years had had severe pains in the legs and cramp-like contractions. For nine years he had had stiffness in the knees, inability to run, failing eyesight and inability to walk in the dark. The previous few years he had taken morphin regularly for the pains. Occasionally he had had incontinence of urine and feces.

Physical examination showed the pupils to be mere pinpoints and inactive to light. All reflexes were absent. There was marked swaying in the Romberg position and the gait was ataxic.

The Wassermann reaction in the blood serum and in the spinal fluid was positive. The spinal fluid cell count was 5 per c.mm.

Treatment consisted of five doses of 0.6 gm. of salvarsan at another hospital and six doses of 0.9 gm. of neosalvarsan here at weekly intervals. As no improvement resulted he was later given the Swift-Ellis treatment at another hospital with considerable improvement.

CASE 3.—A man, aged 46, entered the hospital May 8, 1913. A diagnosis of tabes dorsalis was made. The patient had had a chancre twenty-five years before, and had been treated with mercury by mouth for three years. For seventeen years he had had pain in the region of the urinary bladder and inability to pass his urine. For twelve years he had led a catheter life. For fifteen years he had suffered from shooting pains in his arms and legs and for the previous three years he had used about 16 gm. codein and 2.5 gm. morphin daily. Occasionally he had been troubled by diplopia.

Physical examination showed Argyll Robertson pupils. The deep reflexes of the arms and legs were absent and there was noticeable ataxia.

The Wassermann reaction in the blood serum was positive, in the spinal fluid negative. The spinal fluid cell count was 2 per c.mm.

Treatment consisted of six doses of neosalvarsan and six doses of salvarsan given during a period of seven months. There was considerably less pain at the end of this time and it was not necessary to use a catheter so frequently.

CASE 7.—A man, aged 52, entered the hospital Nov. 3, 1913. A diagnosis of cerebrospinal syphilis was made. During the month before entrance he had had severe headaches, dizziness and ringing in the ears. He had also suffered from nausea and vomiting. Several times he had fallen on the street.

Physical examination showed that all his reflexes were hyperactive.

The Wassermann reaction in the blood serum was positive. In the spinal fluid the Wassermann reaction was positive with 0.2 c.c. The cell count in the spinal fluid was 6 per c.mm.

He was given two doses of salvarsan of 0.3 gm. each and three doses of neosalvarsan of 0.9 gm. each. The treatments were given at weekly intervals. The headaches, dizziness and ringing in the ears were considerably relieved after the first two treatments. After the last treatment there was complete relief from all symptoms and there has been no return of any trouble up to the present time.

CASE 30.—A man, aged 32, entered the hospital Jan. 15, 1915. A diagnosis of tabes dorsalis was made. For eight years he had had constipation and pain in the region of his sacrum. For several months he had been unable to empty his bladder and had been repeatedly catheterized.

Physical examination showed a sluggish reaction of his pupils to light, absent knee jerks and a positive Romberg test.

The Wassermann reaction in the blood serum was negative. In the spinal fluid a cell count of 22 per c.mm. was found. The Wassermann reaction in the fluid was positive with 0.2 c.c.

He was given four doses of salvarsan of 0.5 gm. each. There was no improvement in his symptoms and there was no change in the findings in the spinal fluid.

CASE 37.—A man, aged 30, entered the hospital June 28, 1915. A diagnosis of syphilitic meningitis was made. He had had a chancre eight months before coming to the hospital, which was followed by a generalized rash, sore throat and alopecia. He had taken mercury by mouth and potassium iodid for five months. For ten days he had had severe pains across the abdomen and extremely severe headaches, which had prevented sleep.

Physical examination showed a stiff neck and positive Kernig's sign. The Achilles tendon was absent on the right. His temperature was 104 F. and his pulse rate averaged about 120 per minute.

The Wassermann reaction was positive in both blood and spinal fluid. The cell count in the spinal fluid was 940 per c.mm. A differential count showed 62 per cent. of these cells were small mononuclears, 35 per cent. large mononuclears and 3 per cent. polymorphonuclears.

He was given five doses of salvarsan. After the first three doses all symptoms disappeared. The spinal fluid cell count was reduced from 940 to 33. The Wassermann reaction in the spinal fluid was changed from positive with 0.5 c.c. to positive with 1 c.c. The last treatment was five months ago. The patient has not been heard from since that time.

CASE 52.—A man, aged 21, entered the hospital Sept. 10, 1915. A diagnosis of cerebrospinal syphilis was made. For four years he had had headaches and occasional attacks of dizziness. The headaches had increased in severity during the previous year and later he had had attacks of vomiting. Ten days before weakness and stiffness of the right arm had appeared and his vision had become blurred. Six days before he had suddenly become unable to talk and he had noticed also that the right side of his face had become paralyzed. During the previous two days he had noticed some improvement, although he had had no treatment except rest in bed.

Physical examination showed marked weakness of the extensor muscles of the right arm. The reflexes of both arms and of the right leg were greatly exaggerated. The reflexes of the left leg were not increased. There were posi-

tive Babinski, Oppenheim and Gordon signs on both sides. There was a marked disturbance of his speech.

The Wassermann reaction was positive in both blood and spinal fluid. The cell count in the spinal fluid was 98 per c.mm.

He was given six doses of 0.5 gm. salvarsan at weekly intervals. After the first three doses all of his symptoms were relieved and the cell count in his spinal fluid was reduced to 60 per c.mm. The next three doses of salvarsan reduced the cell count to 9. The Wassermann reaction in the spinal fluid previously positive with 0.3 c.c. became negative with 2 c.c., but the blood serum remained positive. Four months have elapsed since treatment.

Case 63.—A woman, aged 45, entered the hospital Nov. 24, 1915. A diagnosis of cerebrospinal syphilis was made. The patient had had a chancre five years before. Two years before she had had some loss of strength and periods during which she was incontinent of both urine and feces. One month previous to entrance she had had a sudden attack of weakness of the left leg. Two weeks later she had developed intense headaches which had prevented sleep and had confined her to bed. Her eyesight had failed rapidly.

Physical examination showed unequal pupils, which reacted sluggishly to light. All the deep reflexes of the arms and legs were hyperactive, particularly on the left side. There was some ataxia in the movements of the left arm and hand.

The Wassermann reaction in both blood and spinal fluid was positive, with a cell count in the latter of 42 per c.mm.

She was given nine doses of 0.4 gm. salvarsan at weekly intervals. The first two doses of salvarsan relieved her headache and improved the condition of her leg to some extent. After five doses of salvarsan she became able to walk on the street and only the closest inspection revealed any spasticity of the left leg. The Wassermann reaction in the spinal fluid was not modified, but the cell count was reduced from 42 to 4 per c.mm. After four more doses of salvarsan the Wassermann reaction in the spinal fluid was changed from positive with 0.1 c.c. to positive with 0.3 c.c. There was no effect on the Wassermann reaction in the blood serum.

Case 71.—A man, aged 33, entered the hospital Dec. 10, 1915. A diagnosis of cerebrospinal syphilis was made. Four years before he had had a chancre. He had developed a generalized rash five months before with general weakness, headache and pain in his legs.

Physical examination showed a generalized maculopapular rash and general glandular enlargement. In addition he had some photophobia and all the deep reflexes of the arms and legs were exaggerated.

The Wassermann reaction in the blood serum and in the spinal fluid with 0.8 c.c. was positive. The cell count in the spinal fluid was 51 per c.mm.

Treatment consisted of six doses of 0.6 gm. of salvarsan at weekly intervals. At the end of this course of treatment the rash had disappeared and all of his symptoms had cleared up. The Wassermann reaction in the spinal fluid became negative with 1.5 c.c. of fluid, and the cell count dropped from 51 to 7 per c.mm. The Wassermann reaction in the blood serum was not altered.

Case 72.—A man, aged 45, was admitted to the hospital Dec. 14, 1915. A diagnosis of cerebrospinal syphilis was made. Twenty years before he had had a chancre, which was followed by a generalized rash and some loss of hair. He had had no treatment other than two months of mercury by mouth. He had had no further manifestations of syphilis up to one year before, when his vision began to fail.

Physical examination showed an inequality of pupils with exaggerated deep reflexes in both legs.

The Wassermann reaction in both blood serum and spinal fluid was positive. The cell count in the spinal fluid was 30 per c.mm.

He was given five doses of 0.6 gm. salvarsan without any change in his symptoms or signs and without any effect on his cell count or Wassermann reactions. At the end of this time he was treated by the Swift-Ellis method.

TREATMENT WITH SALVARSANIZED SERUM INTRASPINALLY ALONE

CASE 4.—A man, aged 38, entered the hospital Oct. 9, 1913. A diagnosis of tabes dorsalis was made. Sixteen years before he had had a chancre and had been treated with mercury by mouth for nine months. Ten years before he had had a sore mouth and had been treated with mercury and with potassium iodid for nine months. Nine months before he had had an ulcer in his throat, had felt run down and tired out. Because of this he had been treated for several months with mercury by mouth and intramuscularly but without relief. During the four months before entrance he had been given twelve doses of neosalvarsan of 0.9 gm. each. The first four doses had for a short time relieved his symptoms, he had then begun to have pain in the back of his head and neck, and in his legs and abdomen. All of this trouble had developed while he was being treated vigorously with mercury and salvarsan and consequently he had become very despondent.

Physical examination showed no signs of disturbance in his reflexes. The Wassermann reaction was negative in his blood serum and also in his spinal fluid with 0.5 c.c. The spinal fluid showed a cell count of 10 per c.mm., and gave a doubtful globulin test (Noguchi). He was discharged from the hospital, with a diagnosis of overtreatment and apprehension.

He was readmitted Jan. 19, 1914. At that time he stated that he had had no treatment since the previous admission, that all his symptoms had become steadily worse, that he had developed very severe headaches, that he had been restless and irritable and had repeatedly thought of committing suicide because of the agonizing pains in his legs, neck and head.

Physical examination showed small irregular pupils, which reacted very little to light, and some drooping of the left eyelid. He was evidently very much upset, very nervous and irritable.

The spinal fluid showed a cell count of 15 per c.mm. and gave a positive globulin test (Noguchi). The Wassermann reaction was positive with 0.4 c.c.

On January 22 he was given the first treatment with salvarsanized serum. The cells in the spinal fluid were reduced from 15 to 10 per c.mm. and the headaches were improved. On January 29 the second treatment was given. After this the pains began to diminish in frequency and intensity. On February 4 the third treatment was given. This entirely relieved him of headaches. The cell count in his spinal fluid was reduced to 4 per c.mm. The spinal fluid gave a positive Wassermann reaction with 0.5 c.c. On February 11 a fourth treatment was given. Following this he had a few indefinite pains. At this time a decided mental change could be noted. Instead of staying in bed all day he became anxious to get up and about and seemed much encouraged. On February 13 he was given 0.3 gm. of salvarsan intravenously. This was followed by a bad reaction. The cell count in his spinal fluid rose to 15 per c.mm and he went back to bed. He refused to take more salvarsan after this experience. On February 18 he was given the fifth intraspinal treatment. On February 25 he was given the sixth treatment and following this he began to improve again. The cell count in his spinal fluid at this time was 10 per c.mm. He was given additional intraspinal treatment on March 5, 12, 19 and 26. After the treatment on March 26 the spinal fluid cell count was positive with 0.6 c.c. He was then discharged, although he still complained at times of slight pain in his arms. Additional intraspinal treatment was given on April 5, 12, 19 and 26. After that time he became free from all symptoms, gained weight and walked several miles daily. Further treatment was given on May 3, 9 and 16. After the treatment on May 16 he began to work regularly. The spinal fluid showed a normal cell count and gave a positive Wassermann reaction with 0.8 c.c. On May 24 he was given the eighteenth intraspinal treatment and on June 5, 13, 23 and 30, on July 7 and 26 and on August 16 he was given further treatment intraspinally. The treatment on August 16 was his twenty-fifth. After that time he worked days and night as a police detective, walking from six to

fourteen miles daily. He ate and slept irregularly, but had no symptoms, and felt better than he had for several years. The spinal fluid showed a normal cell count and gave a positive Wassermann reaction with 1 c.c. Treatment was then omitted for two months. On October 10 he was given the twenty-sixth treatment, and on December 12 the twenty-seventh. At that time his spinal fluid gave a negative Wassermann reaction with 1 c.c. and showed a normal cell count. On Jan. 19, 1915, he was given additional treatment. Three months later, April 18, he was given the twenty-ninth treatment. The spinal fluid at that time showed a cell count of 2 per c.mm., the Wassermann reaction was negative with 2 c.c., and the globulin test and the colloidal gold test were negative. He had no symptoms of any kind.

A total of twenty-nine intraspinal treatments were given, the first twenty-three at weekly intervals. The first four treatments relieved the severe pains in his head, neck, abdomen and legs, headache and sleeplessness, only indefinite pains remaining. He was out of bed and walking about the ward. The spinal fluid showed a reduction in cells from 15 to 4. The Wassermann reaction was changed from positive with 0.4 c.c. to positive with 0.5 c.c. The next six treatments reduced the cells to 1 per c.mm. and the patient was able to go home with only occasional indefinite pains, and he began to take long walks. The next six treatments reduced the Wassermann reaction to positive with 0.8 c.c. The patient began to work and to put on weight. The next eight treatments reduced the Wassermann reaction to positive with 1 c.c. Treatments were given at two monthly intervals for the next two times. The Wassermann reaction became negative with 1 c.c. The globulin test and the colloidal gold test were negative and the patient was free from all symptoms. The pupils did not return to normal. Thus, the symptoms cleared up and the cell count returned to normal quickly, but the Wassermann reaction became negative more slowly. Although an early case, it is interesting to note the rapid changes in symptoms and in pupils during the three months interval between the first two admissions. A more interesting point is that the patient grew worse while under intensive treatment with neosalvarsan and intramuscular mercury, but four intraspinal treatments relieved the symptoms. Twelve months have elapsed since the last treatment. The patient has worked every day and is free from symptoms. The Wassermann reaction in the blood serum is negative and in the spinal fluid it is negative with 2 c.c.; the cell count is 2 per c.mm.

Case 12.—A man, aged 45, entered the hospital Nov. 3, 1913. A diagnosis of cerebrospinal syphilis was made. He had had a chancre eight years before. For two years he had had mucus discharge from his nose and photophobia. For the previous year he had had failing vision, until at entrance he could make out only moving objects close to his eyes. He had had dizziness and nausea. He had taken quantities of mercury and potassium iodid and many doses of salvarsan without effect. He had been entirely incapacitated for work.

Physical examination showed hypertrichosis, optic atrophy, pupils which reacted to light, deafness in the left ear, enlargement of the hands, wrists and ankles.

The Wassermann reaction in the blood serum was negative, in the spinal fluid it was positive with 0.3 c.c. The spinal fluid cell count was 15 per c.mm.

At weekly intervals he was given thirteen intraspinal treatments and with the last three intraspinal injections he was given three doses of salvarsan. After the treatment outlined the Wassermann reaction changed from positive with 0.3 c.c. to positive with 0.7 c.c. and the cell count in the spinal fluid varied between 43 and 9. There was relief of headache and slight improvement in vision. The improvement lasted for eight months. The Roentgen-ray findings together with the symptoms and signs pointed to acromegaly and the above treatment was undertaken to rule out a possible syphilitic basis. There was insufficient evidence of pituitary tumor to warrant any operation except decompression. Two years have elapsed since the last treatment and he has worked every day.

Case 22.—A man, aged 42, entered the hospital, and on examination a diagnosis of tabes dorsalis was made. He had had a chancre twenty-three years before, followed by a rash, sore throat and alopecia. He had been treated with mercury by mouth for three years. Twelve years before he had begun to have shooting pains in his legs. Seven years before he had noticed that he could not run and that he had difficulty in walking at night. He had taken twenty doses of salvarsan in the previous two years, each treatment helping for a short time only.

Physical examination showed unequal pupils, which did not react to light, absent deep reflexes in the legs, positive Romberg test and ataxia of the hands and feet.

The Wassermann reaction in the blood serum was negative; in the spinal fluid it was positive with 1 c.c. and there was a cell count of 7 per c.mm.

The patient was given nine doses of salvarsanized serum intraspinally. The first intraspinal treatment produced a provocative Wassermann reaction in the spinal fluid, a positive reaction with 1 c.c. becoming positive with 0.5 c.c. The eight following treatments changed the Wassermann reaction back to positive with 1 c.c. Pain, numbness, and ataxia were relieved, but following the last treatment there was a slight return of the ataxia which is clearing up.

Case 23.—A man, aged 18, entered the hospital Nov. 29, 1914. A diagnosis of syphilitic meningitis was made. Six months before he had had two primary sores, followed by a rash. He had taken mercury and potassium iodid for three months and had had three intravenous doses of salvarsan just previous to entrance to the hospital. For one month he had had a sore throat, sore eyes, headache, pain in his chest and abdomen, vomiting, internal strabismus of the right eye, diplopia, and poor vision. For one week he had had nocturia and dizziness and for four days he had had weakness of the right leg, tremor of the left hand and severe headache. The three doses of salvarsan had not relieved any of his symptoms.

Physical examination showed a retinitis and internal strabismus of both eyes, ptosis of the right eye, left knee jerk exaggerated and greater than the right, neck stiff and painful, Oppenheim positive on the right side, double Kernig, Romberg slightly positive, ankle clonus on the left side and ataxia of the arms and legs.

The Wassermann reaction in the blood serum was negative; in the spinal fluid it was positive with 0.1 c.c. The spinal fluid cell count was 550 per c.mm.

On November 29, December 5 and December 9 he was given salvarsan 0.2 gm., 0.4 gm. and 0.6 gm. intravenously and during this time he was given six doses of intramuscular mercury and 30 drops of saturated solution of potassium iodid three times daily. During this two weeks of treatment the headache and diplopia became less, but there were no changes in the physical signs or in the spinal fluid cell count.

December 10 he was given the first intraspinal treatment. This entirely relieved his headache and diplopia. On December 15 the second treatment was given. The cells were reduced from 533 to 272 per c.mm and the stiffness of

the neck and positive Kernig's sign disappeared. He was let out of bed and discharged from the hospital. On December 22 the third treatment was given and the cells were reduced to 100 and there were no symptoms remaining. The Wassermann reaction was positive with 0.2 c.c. On December 29 the fourth treatment was given. The patient went to five dances the following week and danced every dance. On January 1 the fifth treatment was given. He then began to work. On January 12 and 19 the sixth and seventh treatments were given. They were followed by severe headache and pains. On January 26 the eighth treatment was given. On February 2 the cells were 42 and the Wassermann reaction was positive with 0.4 c.c. Although free from symptoms and with the Wassermann reaction diminishing, the cell count varied between 40 and 50 for four weeks, therefore treatments were given less frequently. On February 16 the cells were 14; on March 2 they were 10 and the Wassermann reaction was positive with 0.5 c.c. On March 13 the patient was given the twelfth treatment, and the cells were reduced to 5. During that week the patient had three convulsions. On March 25 he was given the thirteenth treatment, the cells being 7. On April 10 he was given the fourteenth treatment; the cells were 9 and the Wassermann reaction was positive with 0.6 c.c. On May 1 the fifteenth treatment was given. The spinal fluid cell count was 6 per c.mm. On June 5 the sixteenth, and on July 8 the seventeenth treatment was given. The spinal fluid at this time showed a cell count of 6 per c.mm. and gave a negative Wassermann reaction with 1 c.c., but the blood Wassermann reaction became positive. Therefore salvarsan was given for five doses, until the blood serum became negative, and the spinal fluid remained negative with a cell count of 3. Four months have elapsed since the treatment and there has been no return of symptoms. The patient has worked every day.

It is seen that salvarsan, mercury and potassium iodid did not prevent the symptoms of syphilitic meningitis previous to entrance to the hospital, neither did similar intensive treatment improve symptoms of the spinal fluid findings in the hospital; yet two intraspinal treatments relieved all the patient's symptoms, reduced the cell count to 100 and he was able to go home. The third treatment reduced the cells to 50 and he returned to work. Although he was free from symptoms and the Wassermann reaction was rapidly becoming negative, the cells remained between 40 and 50 during the next four treatments, therefore treatments were given less frequently. The next seven treatments rendered the Wassermann reaction negative in 1 c.c. amounts, the cell count normal and the patient was to be given no further treatment; but it was found that the blood repeatedly negative had become positive, so that six doses of salvarsan were given until the blood become negative. The evidence of active syphilis in the blood may explain the convulsions while he was under intraspinal treatment. The fact that the blood previously negative should become positive while under intraspinal treatments is interesting. A similar occurrence has been noted in one other case in this series.

Case 24.—A man, aged 41, entered the hospital June 26, 1914. A diagnosis of tabes dorsalis was made. He had had a chancre twelve years previously. For the past four years he had had attacks of abdominal pain at first at from five to six months' intervals and these had gradually become more frequent until during the previous year the attacks had occurred every month and for

the previous few months the attacks had come every week. These attacks of pain usually lasted several days, were paroxysmal in type, sharp and knifelike and were accompanied by retching and vomiting. He had marked constipation, the bowels not moving oftener than once a week. Two doses of salvarsan had been given at another hospital without relief of the pain or vomiting and he had been operated on for intestinal obstruction. The patient entered this hospital during an attack of gastric crisis.

Physical examination showed that the pupils were irregular and inactive to light, that there was some deafness in the right ear and that all deep reflexes of the arms and legs were hyperactive. Bismuth Roentgen-ray studies of the intestinal tract showed marked contraction and deep peristaltic waves. The Wassermann reaction in the blood serum was negative, but in the spinal fluid it was positive with 0.4 c.c., with a spinal fluid cell count of 5.

On June 18 during an attack of gastric crisis the patient was given intravenous salvarsan without relief, but on June 25 during another attack of gastric crisis the patient was given salvarsanized serum intraspinally, and in a few hours the pain and vomiting were relieved, the bowels moved every day thereafter and bismuth Roentgen ray gave normal intestinal findings. After a second intraspinal treatment on June 30 he was free from gastric crisis for three weeks, during which time he was able to eat everything and he gained 11 pounds in weight. On July 28 the gastric crisis returned and again salvarsan was given without relief. On August 8 during an attack of gastric crisis a third intraspinal treatment relieved all symptoms and the bowels became regular. On August 21, following a fourth intraspinal treatment, all symptoms were relieved for four weeks. For the next five months the patient was practically free from pain, at the end of which time he was given a fifth treatment and the spinal fluid showed 3 cells and a positive Wassermann reaction with 0.7 c.c. Following this treatment he had a severe reaction lasting for one day and the spinal fluid cell count increased to 87. On February 2 a sixth treatment was given, on February 9 a seventh, and on February 16 the eighth and final treatment was given. After this treatment the patient was free from pain, the cells in the spinal fluid became normal and the Wassermann reaction in the spinal fluid became negative with 1 c.c.

In this case on three separate occasions intravenous salvarsan had no influence on the gastric crisis, but intraspinal treatment promptly relieved all symptoms for three and four weeks' duration and later treatments entirely relieved the severe pain. The Wassermann reaction in the spinal fluid was changed from positive with 0.4 c.c. before treatment to negative with 1 c.c. after eight treatments. One year has elapsed since treatment was stopped and the patient has been free from gastric crises.

Case 25.—A man, aged 48, entered the hospital Aug. 14, 1914. A diagnosis of tabes dorsalis was made. For five years he had had lightning pains in the abdomen and in the legs; for the previous two years he had had a constriction around the waist, dizziness, ataxia in the dark and inability in starting his urine; for the previous eight months he had had numbness of the left hand, severe girdle pains, failing eyesight and incontinence of urine and feces. He entered the hospital because of unbearable girdle pains.

Physical examination showed that the right pupil was larger than the left and inactive to light, and that both disks were of a chalky white; that the knee jerks were absent, and the Romberg was positive. There was ataxia and incoordination of the left leg, and areas of anesthesia were present over both legs. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.2 c.c. The spinal fluid cell count was 20.

On August 14 the first intraspinal treatment was given and the girdle pains were relieved and the cells in the spinal fluid were reduced to 3. On August 19 a second treatment relieved the dizziness and numbness and the cell count remained 3. On August 28 a third treatment was given; at this time the patient was less ataxic and felt stronger and the cell count was 0. On September 5 a fourth treatment was given, all symptoms were relieved and the patient was able to walk well. Following a fifth treatment on September 22 further treatment was omitted for two months. At the end of this time, on November 19, he was given a sixth treatment and was still free from all symptoms; he had no incontinence of urine and feces and the cell count was 6. On January 5 the seventh treatment was given and the patient had begun to work. On February 16 the eighth treatment was given and the patient was able to walk without trouble in the light and could walk very well in the dark; the cell count was 3. Treatment was omitted for four months. On June 10, although he was still free from symptoms, a ninth treatment was given, the cell count was 4. On July 8 a tenth treatment was given; the patient was free from symptoms, the cell count was 3, but the spinal fluid was positive with 0.2 c.c.

The first intraspinal treatment reduced the spinal fluid cell count from 20 to 3 and relieved the severe girdle pains; the first four treatments relieved all symptoms except the incontinence of urine and feces and these were relieved following the sixth treatment. Ataxia and incoordination rapidly improved. In spite of the marked improvement and the relief of all symptoms and a constant normal cell count, still the Wassermann reaction in the spinal fluid was uninfluenced by ten intraspinal treatments. This is contrary to the findings in the other cases. Ten months have elapsed since treatment, with no return of symptoms.

Case 26.—A man, aged 35, entered the hospital Oct. 8, 1914. A diagnosis of tabes dorsalis was made. Fifteen years previously he had had a chancre followed by a rash and sore throat and had been treated with potassium iodid and mercury by mouth for three months. For the previous ten years he had had shooting pains in the legs every four or five weeks; for the previous two years he had had ataxia and failing vision, both of which were worse at night; for the past few months he had had partial paralysis and numbness of the right side of the body and occasional attacks of vomiting. The difficulty in walking had gradually increased until at the time of entrance he was unable to walk alone and the severe pains in the chest and the abdomen were constant, the pains in the legs occurring nearly every day.

Physical examination showed that the left eye did not react to light, that there was ptosis of the right eyelid and that there was internal strabismus and partial optic atrophy of both eyes. The knee jerks, the abdominal and the cremasteric reflexes were absent and there was a suggestive Babinski sign. Romberg sign was positive, there was incoordination of the left hand and arm and the patient was unable to walk alone. The Wassermann reaction in the blood serum was questionable and in the spinal fluid it was positive with 0.2 c.c., with a spinal fluid cell count of 40.

On October 10 the first intraspinal treatment with salvarsanized serum was given. On October 17 the second treatment relieved all pain and reduced the cell count to 14. On October 26 the third treatment was given and the cells in the spinal fluid were reduced to 5 and the patient felt well. On November 3 the fourth treatment was given and the spinal fluid showed a positive Wassermann reaction with 0.3 c.c. and a cell count of 16; on account of the latter condition

treatment was omitted for one month. On December 8 and 15 the fifth and sixth treatments were given. The patient was still free from pain, was less depressed and the paralysis and numbness were relieved. The cell count was 4, but he was more ataxic. On December 22, 29 and January 5 he was given the seventh, eighth and ninth treatments. The spinal fluid cell count was 1 and the Wassermann reaction was positive with 0.4 c.c. Although the patient was free from pain and was able to see better, the cell count was only 1 and the Wassermann reaction was weaker, still he was more ataxic and consequently further treatment was postponed. During the next few months the ataxia gradually decreased until the patient could walk with the aid of a cane, could drive horses and an automobile and was able to attend to a country medical practice. His eyesight improved so much that he discarded his glasses. On August 5, seven months after the last treatment, he was given the tenth intraspinal treatment and the spinal fluid showed 2 cells and a negative Wassermann reaction with 1 c.c. On August 12 he was given the eleventh treatment. Because his blood Wassermann reaction had always been questionable he was given two doses of salvarsan of 0.3 gm. each and further treatment was discontinued.

The first three treatments relieved all pain, numbness and vomiting and the spinal fluid cell count was reduced from 40 to 5. Five treatments were required to change the Wassermann reaction from positive with 0.2 c.c. to a positive with 0.3 c.c., and five more treatments were required to change it from 0.3 c.c. positive to 0.4 c.c. positive. Although the patient was relieved of all symptoms except ataxia, the latter progressively increased. During the next few months, however, without treatment the ataxia gradually decreased until he was able to conduct his practice. Thirteen months have elapsed without return of symptoms; the patient is able to walk unassisted and the spinal fluid shows a cell count of 1 and the spinal fluid Wassermann reaction is negative with 1 c.c.

CASE 27.—A man, aged 35, entered the hospital Oct. 14, 1914. A diagnosis of tabes dorsalis was made. Eight months before he had noticed that his knees were stiff on going up stairs, and a little later that he staggered when walking on a level. At this time he also noted a constriction about the abdomen and paresthesia in the legs, and he was very irritable. Six months before entrance he had developed incontinence of urine, had had difficulty in writing, and in buttoning his clothes, had been unable to keep his balance with his eyes closed and had had some dizziness. For the previous four months he had had sharp, shooting pains in the legs and has become helpless in the dark. For the previous two months he had been unable to walk alone and only with great difficulty when taking some one's arm. He was unable to walk at all on an uneven surface.

Physical examination showed that all deep and superficial reflexes were absent and Romberg test was positive; in fact he could not stand alone. There was marked ataxia and incoordination of the arms and legs. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.4 c.c., and the spinal fluid cell count was 210.

On October 22 the first treatment of salvarsanized serum was given and the cell count was reduced to 100. On October 28 the second treatment relieved dizziness, lessened the pain and reduced the cells to 37. On November 4 the third treatment was given and improvement in walking was noted. On November 11 the fourth treatment caused a severe reaction with excessive pain, and the cell count increased to 165, so that treatment was omitted for three weeks. On December 2 the fifth treatment relieved the pain, reduced the cell count to 50

and the Wassermann reaction became positive with 0.5 c.c. On December 9, 15 and 22, respectively, the sixth, seventh and eighth treatments were given, during which time the cell count varied between 36 and 50. The last treatment caused a severe reaction, so treatment was omitted for two weeks. On January 5 the ninth treatment was given and it was noted that the patient could walk better and that the spinal fluid Wassermann reaction was positive with 0.7 c.c. On January 12 the tenth treatment caused a bad reaction and the cell count increased to 75. As this had happened three different times further treatment was given at two-week intervals. On January 26 the eleventh treatment was given and the patient was free from pain and could walk a little alone, the spinal fluid showing 33 cells and a positive reaction with 0.8 c.c. On February 9 the twelfth treatment was given and the patient was able to walk on the street alone. On February 24 the thirteenth treatment was given and on March 9 the fourteenth treatment; the spinal fluid showed 16 cells and a positive Wassermann reaction with 1 c.c., and the patient could walk with a cane at will. On April 1, 15, and May 12 treatments were given; the patient was able to walk without a cane, the spinal fluid showed 8 cells and a negative Wassermann reaction with 1 c.c. On June 2 and 23 the eighteenth and nineteenth treatments were given. Six weeks later, on August 5, the twentieth treatment was given and on August 12 the twenty-first and last treatment was given. At this time the spinal fluid showed 5 cells and a negative Wassermann reaction with 2 c.c. The patient began to work and has continued to do so since the last treatment, eight months ago without untoward symptoms.

This case was evidently one of rapid onset and of a very active process, since only one and one half years elapsed between the first minor symptom of stiffness and the final symptom of paralysis; the activity of the process is further evidenced by the high cell count of 210 for a case of tabes. The first three treatments relieved the pains and dizziness and were followed by slight improvement in the paralysis and by a reduction in the spinal fluid cells from 210 to 37. On account of the severe reactions following treatment the interval between these was increased from one to two weeks. When these severe reactions occurred the spinal fluid cells increased, although the Wassermann reaction steadily improved. Following the two week interval between treatments, no bad reactions resulted, the cell count slowly became normal, the Wassermann reaction rapidly became negative and the patient rapidly improved in locomotion until he was able to work. It required twenty treatments to render the patient able to walk a mile without aid and to reduce the spinal fluid cells to normal and to give a negative Wassermann reaction with 2 c.c. Eight months have elapsed since the last treatment, and he has had no return of symptoms and has worked every day since.

Case 31.—A negro woman, aged 33, entered the hospital Oct. 22, 1914. A diagnosis of tabes dorsalis was made. Sixteen years previous she had had a generalized rash which disappeared under mercury treatment by mouth. For the previous three years she had noticed that she became very nervous and that her eyesight was failing. Two years before she had begun to have shooting pains in the head and eyes; one year before the shooting pains had appeared in her legs. Four years before her entrance she had begun to develop a staggering gait. At the time of admission she was unable to walk alone, was able

to see only the fingers held close to her eyes, was unable to sleep because of the very sharp pains in her legs.

Physical examination showed that the pupils did not react to light and that optic atrophy was present in both eyes. The deep arm reflexes were hyperactive and the deep leg reflexes were absent. Romberg test was positive and the patient was barely able to stand alone. In the blood serum the Wasserman reaction was negative and in the spinal fluid it was negative with 1 c.c., and the cell count was 27 per c.mm.

An intraspinal injection of salvarsanized serum on October 22 caused a severe reaction of pain, but reduced the cells in the spinal fluid from 27 to 13. On November 3 a second treatment relieved all pain, so that the patient could sleep well and the cells were further reduced to 7. On November 17, a third treatment was given, and the patient was able to see large objects which could not be seen previously; she could walk alone, in fact walked into the hospital unassisted. Fourteen months have elapsed since the last treatment.

Case 32.—A woman, aged 38, entered the hospital Dec. 22, 1914. A diagnosis of tabes dorsalis was made. For the previous two years she had had sharp pains over the whole body and gradually the pains had increased in frequency until at entrance to the hospital they were constant in the legs and abdomen and were so severe as to prevent sleep, and large doses of aspirin gave little relief. The skin had become sore to the touch and the patient had become very nervous and irritable. She had had occipital headaches of a week's duration for some time.

Physical examination showed that both pupils were pinpoint and inactive to light. The deep and the superficial reflexes were absent in both arms and legs. In the blood serum the Wassermann reaction was negative and in the spinal fluid it was negative with 1 c.c.; the spinal fluid showed a cell count of 60 per c.mm.

On December 29 an intraspinal injection of salvarsanized serum nearly relieved the pain and did relieve the headache and reduced the spinal fluid cell count from 60 to 23. Following a second treatment, on January 5, all pain was relieved and the patient was able to eat and sleep well and she felt well. Following a third treatment, on January 19, the spinal fluid cell count became normal and the patient was still free from all symptoms. Thirteen months have now elapsed.

Case 33.—A man, aged 38, entered the hospital Oct. 17, 1914. A diagnosis of tabes dorsalis was made. He had had a chancre eight years before. For the previous year he had had diplopia and general weakness, both of which symptoms had been temporarily relieved by injections of salvarsan. Treatment with salvarsan was soon followed by numbness over the abdomen and a dragging sensation in the perineum and by incontinence of urine. These symptoms were relieved by four injections of salvarsanized serum intraspinally. At entrance to the hospital he complained of numbness in the fingers of the left hand, numbness and loss of sensation on the left side of the abdomen, girdle sensation, loss of sexual power, sensation of walking on cotton and inability to run and jump.

Physical examination showed that the pupils reacted slightly to light and that the deep reflexes of the arms and legs were absent. The Romberg test was slightly positive. The Wassermann reaction in the blood serum was negative, in the spinal fluid it was positive with 0.6 c.c. The spinal fluid cell count was 3.

On October 31, November 21 and December 12, respectively, three intraspinal injections of salvarsanized serum were given. The numbness and the sensation of walking on cotton were relieved and the spinal fluid showed 3 cells per c.mm. and a positive Wassermann reaction with 0.8 c.c. On January 9 a fourth treatment relieved the girdle sensation and on February 6 a fifth treatment showed the spinal fluid cell count to be 1, sexual power had returned and the patient felt well. On March 20 a sixth treatment was given and the spinal

fluid was negative with 1 c.c., but the blood serum, which had been found to be negative previously, on this date gave a positive reaction, so that the patient was given six doses of salvarsan intravenously. At the expiration of four months the patient was free from symptoms and the spinal fluid gave a negative reaction with 1 c.c. but as the blood was still positive further treatment with salvarsan was given.

Case 34.—A man, aged 35, entered the hospital Jan. 14, 1915. A diagnosis of tabes dorsalis was made. He had had rheumatic pains in the joints for several years. During the year previous to entrance he had become very nervous and irritable. For the previous six months he had had paroxysmal pain in the right side and sharp, stabbing pains in the thighs and knees and pains encircling the waist. For the past few weeks he had had dizziness and increasing unsteadiness in the gait, more noticeable in the dark.

Physical examination showed that the pupils reacted slightly to light, that the deep arm reflexes were hyperactive and that the deep leg reflexes were absent; the Romberg test was positive with marked staggering. The Wassermann reaction in the blood serum was negative, in the spinal fluid it was positive with 0.1 c.c. and there were 88 cells per c.mm.

On January 26 the first intraspinal treatment relieved the girdle sensation. On February 2 the second treatment relieved the dizziness and diminished the intensity of the pains; the spinal fluid cell count was reduced to 26. On February 9 the third treatment entirely relieved the pain, and the patient was able to walk more steadily. On February 16, February 24 and March 9, respectively, the fourth, fifth and sixth treatments were given. The patient was entirely free from symptoms and the spinal fluid showed 3 cells and a positive Wassermann reaction with 0.3 c.c. On March 23 the seventh treatment produced a bad reaction, with headache and vomiting for several days. On April 13 he was free from symptoms, the cell count was 3 and an eighth treatment was given. On June 15, July 10 and September 25, respectively, the ninth, tenth and eleventh treatments were given. During this time the spinal fluid showed a cell count varying between 2 and 4 and the Wassermann reaction was positive with 0.4 c.c.

All pains, nervousness, mental depression and lassitude were entirely relieved and there was no ataxia except on sudden turning. Six months have elapsed since the last treatment, without any return of symptoms and the patient has been able to work for the past eight months.

Case 35.—A man, aged 36, entered the hospital Feb. 9, 1915. A diagnosis of cerebrospinal syphilis was made. He had a chancre twenty years before and had been treated with mercury by mouth and by inunctions for one year. During the previous eight years he had been treated with potassium iodid by mouth and with corrosive sublimate by injections. Two months previous to entrance he had noticed marked sleepiness and a whirling before the eyes. For the previous three weeks he had had a constant dull headache. Two days previous to admission he had had a sudden attack of unconsciousness lasting all night and this was followed by diplopia.

Physical examination showed that both pupils did not react to light; that there was a slight nystagmus and internal strabismus. All deep arm and leg reflexes were very active. The patient slept all the time. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.2 c.c. The spinal fluid cell count was 83.

On February 13 the spinal fluid showed 100 cells per c.mm. and the first treatment was given. On February 15 the cells were 150 per c.mm. and the second treatment was given. On February 21 the third treatment was given and the spinal fluid cell count was reduced to 75 and the headache, diplopia, and external rectus weakness disappeared. On March 2 the fourth treatment was given; the cells became 27 and the patient was practically free from symptoms, being only a little drowsy and sleeping little during the day. On March

24 the fifth treatment was given. The spinal fluid cell count was 12 per c.mm. and the patient was free from all symptoms and was discharged. Ten months have elapsed since treatment was stopped and he has worked every day.

CASE 38.—A man, aged 37, entered the hospital May 3, 1915. A diagnosis of tabes dorsalis was made. He had had a chancre eighteen years before. For the previous two years he had had shooting pains in the legs, and during the last year before entrance he had had transient diplopia, and for the previous seven months ataxia, disturbances in micturition, girdle pains and lightning pains in the legs. For the previous eight days he had had vomiting after the taking of food and hiccuping constantly at the rate of 20 to 30 per minute.

Physical examination showed the pupils to be unequal and inactive to light. All deep reflexes were absent and the Romberg test was markedly positive. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.3 c.c. The spinal fluid cell count was 63 per c.mm.

Large doses of morphin had no influence on the hiccup, which was present during sleep. On May 12 the first intraspinal treatment was given and the vomiting and hiccup were relieved after a few hours. The spinal fluid cell count increased to 103 per c.mm. On May 20 a second treatment was given, the spinal fluid cell count became 48 per c.mm. and the pains, vomiting and hiccup ceased. On May 29, June 3, June 24, and July 25 treatments were given; the spinal fluid cell count dropped to 15 per c.mm. and the patient remained free from all symptoms. On August 5 the hiccup began again and was again relieved in a few hours. On August 23, after a period of five days of hiccuping the eighth treatment was given and the hiccup again disappeared. At this time the spinal fluid showed 6 cells and a negative Wassermann reaction with 1 c.c.

Eight intraspinal treatments changed the Wassermann reaction in the spinal fluid from 0.3 c.c. positive to 1 c.c. negative and changed the spinal fluid cell count from 103 per c.mm. to normal. The treatments temporarily relieved the hiccup on three successive occasions and finally relieved it permanently. The treatments also relieved the pain and vomiting and the ataxia was greatly improved.

CASE 42.—A boy, aged 3½ years, entered the hospital May 10, 1915. A diagnosis of syphilitic meningitis was made. For the previous six months he had had pain in the right ear. For the previous six weeks he had had periodic severe headaches accompanied by projectile vomiting, retraction of neck, fever and loss of weight. Lumbar puncture revealed no organisms and antimeningococcic serum was given without relief. On two successive days lumbar puncture revealed a turbid fluid, but no organisms were found in smears or cultures. On the next day, May 10, he was admitted to this hospital with opisthotonus, a rigid neck, positive Kernig sign, a temperature of 104 and a pulse of 150 per minute. Lumbar puncture revealed a turbid spinal fluid, showing 9,800 cells per c.mm. (62 per cent. lymphocytes, 26 per cent. polymorphonuclears, 12 per cent. endothelial cells), no organisms and a positive Wassermann reaction with 0.1 c.c. The Wassermann reaction in the blood serum was positive.

An intravenous injection of 0.2 gm. salvarsan gave no relief. A few days later, on May 22, the first intraspinal treatment was given and this relieved the opisthotonus, the temperature was reduced to 101 and the spinal fluid cell count was reduced to 7,300 per c.mm. On May 24 a second intraspinal treatment relieved the stiffness of the neck, the positive Kernig sign disappeared, and the spinal fluid cell count was reduced to 2,500. On May 27 the third intraspinal treatment was given, the child appeared normal in every way; the spinal fluid cell count was 126 per c.mm. and the Wassermann reaction was positive with 0.2 c.c. On May 29 0.2 gm. of salvarsan was given; on June 3 a fourth intraspinal treatment was given and the child was discharged apparently well. On June 10, July 1 and July 15, respectively, the fifth, sixth and seventh intraspinal treatments were given. At the end of this time the spinal fluid showed

a normal cell count and a negative Wassermann reaction with 2 c.c. Each treatment consisted of 20 c.c. of undiluted salvarsanized serum. The Wassermann reaction in the blood serum also became negative.

No benefit resulted from repeated lumbar puncture, from the injection of antimeningococcic serum or from the first dose of salvarsan; but the first intraspinal treatment with salvarsanized serum relieved the opisthotonus and reduced the spinal fluid cell count from 9,800 to 7,300, and a second similar treatment relieved all symptoms and further reduced the cell count to 2,500 per c.mm. Nine months have elapsed since treatment was stopped and no return of symptoms have developed. It is quite remarkable that seven intraspinal treatments should accomplish so much. The age of the patient (3½ years), the similarity to tuberculosis meningitis, and the negative Wassermann reaction in both parents add considerable interest to the case.

CASE 66.—A man, aged 41, entered the hospital Dec. 10, 1915. A diagnosis of tabes dorsalis was made. For the previous two years he had had shooting pains and hyperesthesia in the legs. Three weeks before he had had a sudden attack of vertigo and ataxia, both of which passed away in a few months. For the previous week he had had pains in the joints and vomiting.

Physical examination showed that the pupils reacted sluggishly to light; the left was larger than the right. The right knee jerk was absent and the left was hyperactive. There was some ataxia. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.3 c.c. The spinal fluid cell count was 29 per c.mm.

Four intraspinal treatments with salvarsanized serum were given at weekly intervals.

The pains, vertigo and hyperesthesia were relieved and the ataxia was decreased.

NOTE.—All treatments were given and all the laboratory work was done by the authors.

A NOTE ON THE BLOOD FAT BEFORE AND AFTER SPLENECTOMY *

HARRY DUBIN, PH.D., AND RICHARD M. PEARCE, M.D.
PHILADELPHIA

Recently, King[1] and Eppinger[2] found that the removal of the spleen resulted in an increase in total fats and lipoids, an increase in cholesterin, and a decrease in the unsaturated fatty acids, as expressed by the iodin number. In addition there was found in severe anemias a very high iodin number, suggesting that hemolysis in anemia is in some way related to the unsaturated fatty acids.

TABLE 1.—BLOOD FAT BEFORE AND AFTER SPLENECTOMY *

Dog	Before Splenectomy		Ten Days after Splenectomy		Remarks
	Total Fats, Gm.	Iodin Number	Total Fats, Gm.	Iodin Number	
15-55 Serum	2.6	51.6	2.82†	51.5	Blood drawn into oxalate
Cells	2.98	43.7	2.42	52	
15-67 Serum	2.85†	51.6	2.83†	51.5	Blood drawn into oxalate
Cells	2.43	53.4	2.43	49.4	
15-76	5.03	47.6	5.09	47	Blood drawn into alcohol
15-75	5.25	49	5.43	48.2	Blood drawn into alcohol
16-23	5.73	47.4	6.038	49.6	Blood defibrinated
16- 4	7.6	70.1	7.71	66	Blood defibrinated

* The iodin number is calculated on the basis of the total amount of fatty extract found in 100 c.c. of blood; the total fats are calculated per 1,000 c.c. of blood.
† As some hemolysis took place while separating the cells from the serum, there may be some inaccuracy in the relative values given for cells and serum.

As a preliminary step to other investigations of the blood fats which we had in mind, it was thought advisable to repeat some of the work of King and Eppinger, that is, that dealing with the total fats and unsaturated fatty acids. King's technic was followed, except that cholesterol and cholesterol esters were not removed before determining the iodin number. We do not believe, however, that our failure to

* Submitted for publication June 21, 1916.
* From the John Herr Musser Department of Research Medicine of the University of Pennsylvania, Philadelphia.

1. King, J. H.: Studies in the Pathology of the Spleen, THE ARCHIVES INT. MED., 1914, xiv, 145.

2. Eppinger, H.: Zur Pathologie der Milzfunction, Berl. klin. Wchnschr., 1913, 1, 1509.

obtain results in accord with those of King and Eppinger can be explained by this difference in method. Our results are summarized in Table 1.

An examination of the figures in Table 1 reveals the fact that the total fats and the iodin number are practically the same both before and after splenectomy, whereas King and Eppinger report under similar conditions a marked increase in total fats, together with an equally definite decrease in the unsaturated fatty acids, as expressed by the iodin number.

SUMMARY

Analysis, before and after splenectomy, of the blood of dogs shows practically no change in the amount of total fats and unsaturated fatty acids, as expressed by the iodin value.

BOOK REVIEW

THE PHYSIOLOGY OF THE AMINO-ACIDS. By Frank P. Underhill, Ph.D., Professor of Pathological Chemistry, Yale University, New Haven: Yale University Press. Price, $1.35 net.

In his preface the author very justly emphasizes the urgent need for a book or monograph on this subject. He has written a summary for the "busy practitioner and others whose resources for consulting original communications are limited." Professor Underhill has carefully analyzed the existing literature and has produced a work which, in a very concise but thorough manner, brings out the most important facts concerning the proteins and amino-acids. The successive chapters deal with the derivation of amino-acids from proteins, the digestion, absorption and excretion of the amino-acids, and their relation to the organism in health and disease. The mere lists of amino-acids and their formulas and other matter which it is a question of "mental gymnastics" to memorize and which serve for necessary reference only are quickly disposed of, and the following chapters on the physiologic and pathologic chemistry of these substances unfold themselves in logical sequence. The treatment of the subject is that of the finished lecturer, thoroughly conversant with his subject, expounding it to a class of beginners. This is a very excellent method of presentation. For the clinician the book gives an adequate exposition of the scientific aspect of the subject, but is not far-reaching enough on its clinical side. The subjects of intestinal putrefaction, auto-intoxication, acidosis, elimination and retention of the end-products of protein metabolism, protein feeding in disease, etc., are not taken up from the physician's point of view. There are clinicians broad enough to be interested in these subjects quite apart from their immediate practical value in the treatment of disease, but they are very few in number. The majority of medical men naturally desire to have the laboratory worker show them how they may apply the "test tube" knowledge to their patients. For the most part a dead line exists between the activities of scientific and clinical workers, which only few individuals from either side are capable of crossing. Professor Underhill has not succeeded in crossing it. The consequence is that while his book presents a very satisfactory though brief review of the amino-acids and proteins from the point of view of the physiologic and pathologic chemist, it does not cover the relations of these substances to clinical problems in as thorough a manner as might be desired.

There are a moderate number of misprints in this volume. One of the most disconcerting is in the formula for dextrose, given as $C_6H_6O_6$ four times within two pages (pages 111 and 112).

There is a great need for essays on this and kindred subjects for physicians. Professor Underhill's little book may be said to be a pioneer in this direction. However, to disseminate knowledge to large numbers of practitioners, it is believed that more attention must be paid to its clinical application.